



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07K 14/47, 14/715</b>	<b>A1</b>	(11) International Publication Number: <b>WO 97/30084</b> (43) International Publication Date: 21 August 1997 (21.08.97)
<p>(21) International Application Number: PCT/US97/02146</p> <p>(22) International Filing Date: 11 February 1997 (11.02.97)</p> <p>(30) Priority Data: 08/602,228 15 February 1996 (15.02.96) US 08/698,551 15 August 1996 (15.08.96) US</p> <p>(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 Cambridge Park Drive, Cambridge, MA 02140 (US).</p> <p>(72) Inventors: LIN, Lih-Ling; 107 College Road, Concord, MA 01742 (US). CHEN, Jennifer; 833 West Roxbury Parkway, Chestnut Hill, MA 02167 (US). SCHIEVELLA, Andrea, R.; 39 Edward Street, Winchester, MA 01890 (US). GRAHAM, James; 28 Foscott Street, Somerville, MA 02144 (US).</p> <p>(74) Agent: BROWN, Scott, A.; Genetics Institute, Inc., 87 Cambridge Park Drive, Cambridge, MA 02140 (US).</p>		<p>(81) Designated States: AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: TNF RECEPTOR DEATH DOMAIN LIGAND PROTEINS AND INHIBITORS OF LIGAND BINDING</p> <p>(57) Abstract</p> <p>Novel TNF receptor death domain ("TNF-R1-DD") ligand proteins are disclosed. Polynucleotides encoding the TNF-R1-DD ligand protein are also disclosed, along with vectors, host cells, and methods of making the TNF-R1-DD ligand protein. Pharmaceutical compositions containing the TNF-R1-DD ligand protein, methods of treating inflammatory conditions, and methods of inhibiting TNF-R death domain binding are also disclosed. Methods of identifying inhibitors of TNF-R death domain binding and inhibitors identified by such methods are also disclosed.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## TNF RECEPTOR DEATH DOMAIN LIGAND PROTEINS AND INHIBITORS OF LIGAND BINDING

5

This application is a continuation-in-part of application Ser. No. 08/602,228, filed February 15, 1996, which was a continuation-in-part of application Ser. No. 08/533,901, filed September 26, 1995, which was a continuation-in-part of application Ser. No. 08/494,440, filed June 19, 1995, which  
10 was a continuation-in-part of application Ser. No. 08/327,514, filed October 19, 1994.

**BACKGROUND OF THE INVENTION**

The present invention relates to the field of anti-inflammatory  
15 substances and other substances which act by inhibiting binding to the intracellular domain of a tumor necrosis factor receptor (hereinafter "TNF-R"), such as, for example, the P55 type (or TNF-R1) TNF receptor. More particularly, the present invention is directed to novel ligands which bind to the TNF-R intracellular domain and to inhibition or modulation of signal transduction by this receptor.

20 Tumor necrosis factor (herein "TNF") is a cytokine which produces a wide range of cellular activities. TNF causes an inflammatory response, which can be beneficial, such as in mounting an immune response to a pathogen, or when overexpressed can lead to other detrimental effects of inflammation.

The cellular effects of TNF are initiated by the binding of TNF to its  
25 receptors (TNF-Rs) on the surface of target cells. The isolation of polynucleotides encoding TNF-Rs and variant forms of such receptors has been described in European patent publication Nos. EP 308,378, EP 393,438, EP 433,900, EP 526,905 and EP 568,925; in PCT patent publication Nos. WO91/03553 and WO93/19777; and by Schall *et al.*, Cell 61:361-370 (1990) (disclosing the P55 type  
30 TNF receptor). Processes for purification of TNF-Rs have also been disclosed in U.S. Patent No. 5,296,592.

Native TNF-Rs are characterized by distinct extracellular, transmembrane and intracellular domains. The primary purpose of the extracellular domain is to present a binding site for TNF on the outside of the cell. When TNF is bound to the binding site, a "signal" is transmitted to the inside of the cell through the transmembrane and intracellular domains, indicating that binding has occurred. Transmission or "transduction" of the signal to the inside of the cell occurs by a change in conformation of the transmembrane and/or intracellular domains of the receptor. This signal is "received" by the binding of proteins and other molecules to the intracellular domain of the receptor, resulting in the effects seen upon TNF stimulation. Two distinct TNF receptors of ~55 kd ("TNF-R1") and ~75 kd ("TNF-R2") have been identified. Numerous studies with anti-TNF receptor antibodies have demonstrated that TNF-R1 is the receptor which signals the majority of the pleiotropic activities of TNF. Recently, the domain required for signaling cytotoxicity and other TNF-mediated responses has been mapped to the ~80 amino acid near the C-terminus of TNF-R1. This domain is therefore termed the "death domain" (hereinafter referred to as "TNF-R death domain" and "TNF-R1-DD") (see, Tartaglia *et al.*, Cell 74:845-853 (1993)).

While TNF binding by TNF-Rs results in beneficial cellular effects, it is often desirable to prevent or deter TNF binding from causing other detrimental cellular effects. Although substantial effort has been expended investigating inhibition of TNF binding to the extracellular domain of TNF-Rs, examination of binding of proteins and other molecules to the intracellular domain of TNF-Rs has received much less attention.

However, ligands which bind to the TNF-R intracellular domain have yet to be identified. It would be desirable to identify and isolate such ligands to examine their effects upon TNF-R signal transduction and their use as therapeutic agents for treatment of TNF-induced conditions. Furthermore, identification of such ligands would provide a means for screening for inhibitors of TNF-R/intracellular ligand binding, which will also be useful as anti-inflammatory agents.

### SUMMARY OF THE INVENTION

Applicants have for the first time identified novel TNF-R1-DD ligand proteins and have isolated polynucleotides encoding such ligands. Applicants have also identified a known protein which may also bind to the death domain of TNF-R.

5 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide encoding a protein having TNF-R1-DD ligand protein activity. In preferred embodiments, the polynucleotide is selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 2 to nucleotide 1231;
- 10 (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:1;
- (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2;
- (d) a polynucleotide encoding an TNF-R1-DD ligand protein  
15 comprising a fragment of the amino acid sequence of SEQ ID NO:2;
- (e) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 2 to nucleotide 415;
- (f) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:3;
- 20 (g) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4;
- (h) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:4;
- (i) a polynucleotide comprising the nucleotide sequence of SEQ  
25 ID NO:9 from nucleotide 2 to nucleotide 931;
- (j) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:9;
- (k) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10;
- 30 (l) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:10;

(m) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 2 to nucleotide 1822;

(n) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:11;

5 (o) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12;

(p) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:12;

10 (q) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 3 to nucleotide 2846;

(r) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:13, which encodes a protein having TNF-R1-DD ligand protein activity;

15 (s) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14;

(t) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 and having TNF-R1-DD ligand protein activity;

20 (u) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 326 to nucleotide 5092;

(v) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:15;

(w) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16;

25 (x) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:16;

(y) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 14 to nucleotide 2404;

30 (z) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:17;

(aa) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18;

(bb) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:18; and

(cc) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(cc).

5 In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing an TNF-R1-DD ligand protein,  
10 which comprises:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the TNF-R1-DD ligand protein from the culture.

The ligand protein produced according to such methods is also provided by the  
15 present invention.

Compositions comprising a protein having TNF-R1-DD ligand protein activity are also disclosed. In preferred embodiments the protein comprises an amino acid sequence selected from the group consisting of:

- 20 (a) the amino acid sequence of SEQ ID NO:2;  
(b) fragments of the amino acid sequence of SEQ ID NO:2;  
(c) the amino acid sequence of SEQ ID NO:4;  
(d) fragments of the amino acid sequence of SEQ ID NO:4;  
(e) the amino acid sequence of SEQ ID NO:6;  
(f) fragments of the amino acid sequence of SEQ ID NO:6;  
25 (g) the amino acid sequence of SEQ ID NO:10;  
(h) fragments of the amino acid sequence of SEQ ID NO:10;  
(i) the amino acid sequence of SEQ ID NO:12;  
(j) fragments of the amino acid sequence of SEQ ID NO:12;  
(k) the amino acid sequence of SEQ ID NO:14;  
30 (l) fragments of the amino acid sequence of SEQ ID NO:14;  
(m) the amino acid sequence of SEQ ID NO:16;  
(n) fragments of the amino acid sequence of SEQ ID NO:16;

(o) the amino acid sequence of SEQ ID NO:18; and  
(p) fragments of the amino acid sequence of SEQ ID NO:18;  
the protein being substantially free from other mammalian proteins. Such compositions may further comprise a pharmaceutically acceptable carrier.

5 Compositions comprising an antibody which specifically reacts with such TNF-R1-DD ligand protein are also provided by the present invention.

Methods are also provided for identifying an inhibitor of TNF-R death domain binding which comprise:

10 (a) combining an TNF-R death domain protein with an TNF-R1-DD ligand protein, said combination forming a first binding mixture;

(b) measuring the amount of binding between the TNF-R death domain protein and the TNF-R1-DD ligand protein in the first binding mixture;

15 (c) combining a compound with the TNF-R death domain protein and an TNF-R1-DD ligand protein to form a second binding mixture;

(d) measuring the amount of binding in the second binding mixture; and

(e) comparing the amount of binding in the first binding mixture with the amount of binding in the second binding mixture;

20 wherein the compound is capable of inhibiting TNF-R death domain binding when a decrease in the amount of binding of the second binding mixture occurs. In certain preferred embodiments the TNF-R1-DD ligand protein used in such method comprises an amino acid sequence selected from the group consisting of:

- 25 (a) the amino acid sequence of SEQ ID NO:2;  
(b) fragments of the amino acid sequence of SEQ ID NO:2;  
(c) the amino acid sequence of SEQ ID NO:4;  
(d) fragments of the amino acid sequence of SEQ ID NO:4;  
(e) the amino acid sequence of SEQ ID NO:6;  
(f) fragments of the amino acid sequence of SEQ ID NO:6;  
30 (g) the amino acid sequence of SEQ ID NO:8;  
(h) fragments of the amino acid sequence of SEQ ID NO:8;  
(i) the amino acid sequence of SEQ ID NO:10;



- (j) fragments of the amino acid sequence of SEQ ID NO:10;
- (k) the amino acid sequence of SEQ ID NO:12;
- (l) fragments of the amino acid sequence of SEQ ID NO:12;
- (m) the amino acid sequence of SEQ ID NO:14;
- 5 (n) fragments of the amino acid sequence of SEQ ID NO:14;
- (o) the amino acid sequence of SEQ ID NO:16;
- (p) fragments of the amino acid sequence of SEQ ID NO:16;
- (q) the amino acid sequence of SEQ ID NO:18;
- (r) fragments of the amino acid sequence of SEQ ID NO:18.

10 Compositions comprising inhibitors identified according to such method are also provided. Such compositions may include pharmaceutically acceptable carriers.

Methods are also provided for preventing or ameliorating an inflammatory condition which comprises administering a therapeutically effective amount of a composition comprising a protein having TNF-R1-DD ligand protein  
15 activity and a pharmaceutically acceptable carrier.

Other embodiments provide methods of inhibiting TNF-R death domain binding comprising administering a therapeutically effective amount of a composition comprising a protein having TNF-R1-DD ligand protein activity and a pharmaceutically acceptable carrier.

20 Methods are also provided for preventing or ameliorating an inflammatory condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of insulin-like growth factor binding protein-5 ("IGFBP-5"), and fragments thereof having TNF-  
25 R1-DD ligand protein activity. Such proteins may also be administered for inhibiting TNF-R death domain binding.

Methods of preventing or ameliorating an inflammatory condition or of inhibiting TNF-R death domain binding are provided, which comprise administering to a mammalian subject a therapeutically effective amount of  
30 inhibitors of TNF-R death domain binding, are also provided.

Methods of identifying an inhibitor of TNF-R death domain binding are also provided by the present invention which comprise:

(a) transforming a cell with a first polynucleotide encoding an TNF-R death domain protein, a second polynucleotide encoding an TNF-R1-DD ligand protein, and at least one reporter gene, wherein the expression of the reporter gene is regulated by the binding of the TNF-R1-DD ligand protein encoded by the second polynucleotide to the TNF-R death domain protein encoded by the first polynucleotide;

(b) growing the cell in the presence of and in the absence of a compound; and

(c) comparing the degree of expression of the reporter gene in the presence of and in the absence of the compound;

wherein the compound is capable of inhibiting TNF-R death domain binding when a decrease in the degree of expression of the reporter gene occurs. In preferred embodiments, the cell is a yeast cell and the second polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 2 to nucleotide 1231;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:1, which encodes a protein having TNF-R1-DD ligand protein activity;

(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 and having TNF-R1-DD ligand protein activity;

(e) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 2 to nucleotide 415;

(f) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:3, which encodes a protein having TNF-R1-DD ligand protein activity;

(g) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4;

(h) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 and having TNF-R1-DD ligand protein activity;

5 (i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 2 to nucleotide 559;

(j) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:5, which encodes a protein having TNF-R1-DD ligand protein activity;

10 (k) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6;

(l) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 and having TNF-R1-DD ligand protein activity;

15 (m) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 57 to nucleotide 875;

(n) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:7, which encodes a protein having TNF-R1-DD ligand protein activity;

20 (o) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8;

(p) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 and having TNF-R1-DD ligand protein activity;

25 (q) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 2 to nucleotide 931;

(r) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:9;

(s) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10;

30 (t) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:10;

(u) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 2 to nucleotide 1822;

(v) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:11;

5 (w) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12;

(x) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:12;

10 (y) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 3 to nucleotide 2846;

(z) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:13, which encodes a protein having TNF-R1-DD ligand protein activity;

15 (aa) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14;

(bb) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 and having TNF-R1-DD ligand protein activity;

20 (cc) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 326 to nucleotide 5092;

(dd) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:15, which encodes a protein having TNF-R1-DD ligand protein activity;

25 (ee) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16;

(ff) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 and having TNF-R1-DD ligand protein activity;

30 (gg) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 14 to nucleotide 2404;

(hh) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:17, which encodes a protein having TNF-R1-DD ligand protein activity;

5 (ii) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18;

(jj) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 and having TNF-R1-DD ligand protein activity; and

10 (kk) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(jj), which encodes a protein having TNF-R1-DD ligand protein activity.

### **BRIEF DESCRIPTION OF THE FIGURES**

15 Figs. 1 and 2 depict autoradiographs demonstrating the expression of TNF-R1-DD ligand proteins of the present invention.

Fig. 3 depicts an autoradiograph demonstrating the expression of clones 1TU, 15TU and 27TU.

20 Fig. 4 demonstrates the binding of 1TU and 27TU to TNF-R1-DD. MBP, MBP-1TU or MBP-27TU (3 $\mu$ g) was incubated with glutathione beads containing 3 $\mu$ g of either GST or GST-TNF-R1-DD in 100 $\mu$ l of binding buffer (0.2% Triton, 20 mM Tris pH 7.5, 140 mM NaCl, 0.1 mM EDTA, 10 mM DTT and 5% glycerol). The reaction was performed at 4°C for 2 hours and centrifuged to remove unbound fraction (Unbound). The beads were then washed with 500 $\mu$ l binding buffer four times and resuspended into SDS-sample buffer (Bound). These samples  
25 were analyzed by Western blot using anti-MBP antibody (New England Biolab).

30 Fig. 5 demonstrates the ability of 15TU and 27TU to activate the JNK pathway. COS cells were cotransfected with HA-tagged JNK1 and clones 15tu or 27TU. Cells were left untreated or treated for 15 min with 50 ng/ml TNF, and HA-JNK1 was immunoprecipitated with anti-HA antibody. JNK activity was measured in an *in vitro* kinase assay using GST-c-jun (amino acids 1-79) as substrate, and reactions were electrophoresed on SDS-PAGE.

Fig. 6 is an autoradiograph of an SDS-PAGE gel of conditioned media from COS cells transfected with clone 3TW.

Fig. 7 is an autoradiograph which demonstrates that an antisense oligonucleotide derived from the sequence of clone 3TW inhibits TNF-induced cPLA<sub>2</sub> phosphorylation.

### DETAILED DESCRIPTION OF THE INVENTION

The present inventors have for the first time identified and isolated novel polynucleotides which encode proteins which bind to the TNF-R death domain. As used herein "TNF-R" includes all receptors for tumor necrosis factor. The P55 type TNF-R is the preferred receptor for practicing the present invention.

The sequence of a polynucleotide encoding one such protein is set forth in SEQ ID NO:1 from nucleotides 2 to 1231. This polynucleotide has been identified as "clone 2DD". The amino acid sequence of the TNF-R1-DD ligand protein encoded by clone 2DD is set forth in SEQ ID NO:2. It is believed that clone 2DD is a partial cDNA clone of a longer full length coding sequence. However, as demonstrated herein the protein encoded by clone 2DD does bind the death domain of TNF-R (i.e., has "TNF-R1-DD ligand protein activity" as defined herein). Clone 2DD was deposited with the American Type Culture Collection on October 13, 1994 and given the accession number ATCC 69706.

The protein encoded by clone 2DD is 410 amino acids in length. No identical or closely related sequences were found using BLASTN/BLASTX or FASTA searches. Therefore, clone 2DD encodes a novel protein.

The sequence of a polynucleotide encoding one such protein is set forth in SEQ ID NO:3 from nucleotides 2 to 415. This polynucleotide has been identified as "clone 3DD". The amino acid sequence of the TNF-R1-DD ligand protein encoded by clone 3DD is set forth in SEQ ID NO:4. It is believed that clone 3DD is a partial cDNA clone of a longer full length coding sequence. However, as demonstrated herein the protein encoded by clone 3DD does bind the death domain of TNF-R (i.e., has "TNF-R1-DD ligand protein activity" as defined herein). Clone 3DD was deposited with the American Type Culture Collection on October 13, 1994 and given the accession number ATCC 69705.

The protein encoded by clone 3DD is 138 amino acids. No identical or closely related sequences were found using BLASTN/BLASTX or FASTA searches. Therefore, clone 3DD encodes a novel protein.

5 A full-length clone corresponding to clone 3DD was also isolated and identified as "clone 3TW". The nucleotide sequence of clone 3TW is reported as SEQ ID NO:13. Nucleotides 3 to 2846 of SEQ ID NO:13 encode a TNF-R1-DD ligand protein, the amino acid sequence of which is reported as SEQ ID NO:14. Amino acids 811 to 948 of SEQ ID NO:14 correspond to amino acids 1 to 138 of SEQ ID NO:4 (clone 3DD). Clone 3TW was deposited with the American Type  
10 Culture Collection on September 26, 1995 and given the accession number ATCC 69904.

The sequence of a polynucleotide encoding another such protein is set forth in SEQ ID NO:5 from nucleotides 2 to 559. This polynucleotide has been identified as "clone 20DD." The amino acid sequence of the TNF-R1-DD ligand  
15 protein encoded by clone 20DD is set forth in SEQ ID NO:6. It is believed that clone 20DD is a partial cDNA clone of a longer full length coding sequence. However, as demonstrated herein the protein encoded by clone 20DD does bind the death domain of TNF-R (*i.e.*, has "TNF-R1-DD ligand protein activity" as defined herein). Clone 20DD was deposited with the American Type Culture Collection on  
20 October 13, 1994 and given the accession number ATCC 69704.

The protein encoded by clone 20DD is identical to amino acids 87 to 272 of insulin-like growth factor binding protein-5 ("IGFBP-5"), a sequence for which was disclosed in J. Biol. Chem. 266:10646-10653 (1991) by Shimasaki *et al.*, which is incorporated herein by reference. The polynucleotide and amino acid  
25 sequences of IGFBP-5 are set forth in SEQ ID NO:7 and SEQ ID NO:8, respectively. Based upon the sequence identity between clone 20DD and IGFBP-5, IGFBP-5 and certain fragments thereof will exhibit TNF-R1-DD ligand binding activity (as defined herein).

The sequence of a polynucleotide encoding another such protein is set forth in SEQ ID NO:9 from nucleotides 2 to 931. This polynucleotide has been identified as "clone 1TU" The amino acid sequence of the TNF-R1-DD ligand  
30 protein encoded by clone 1TU is set forth in SEQ ID NO:10. It is believed that

clone 1TU is a partial cDNA clone of a longer full length coding sequence. However, as demonstrated herein the protein encoded by clone 1TU does bind the death domain of TNF-R (i.e., has "TNF-R1-DD ligand protein activity" as defined herein). Clone 1TU was deposited with the American Type Culture Collection on  
5 June 7, 1995 and given the accession number ATCC 69848.

The protein encoded by clone 1TU is 310 amino acids in length. No identical or closely related sequences were found using BLASTN/BLASTX or FASTA searches. Therefore, clone 1TU encodes a novel protein.

The sequence of a polynucleotide encoding another such protein is set  
10 forth in SEQ ID NO:11 from nucleotides 2 to 1822. This polynucleotide has been identified as "clone 27TU". The amino acid sequence of the TNF-R1-DD ligand protein encoded by clone 27TU is set forth in SEQ ID NO:12. It is believed that clone 27TU is a partial cDNA clone of a longer full length coding sequence. However, as demonstrated herein the protein encoded by clone 27TU does bind the  
15 death domain of TNF-R (i.e., has "TNF-R1-DD ligand protein activity" as defined herein). Clone 27TU was deposited with the American Type Culture Collection on June 7, 1995 and given the accession number ATCC 69846.

The protein encoded by clone 27TU is 607 amino acids in length. No identical or closely related sequences were found using BLASTN/BLASTX or  
20 FASTA searches. Therefore, clone 27TU encodes a novel protein. 27TU may be a longer version of clone 2DD. 2DD encodes the same amino acid sequence (SEQ ID NO:2) as amino acids 198-607 encoded by 27TU (SEQ ID NO:12). The nucleotide sequences of 2DD and 27TU are also identical within this region of identity.

25 An additional "clone 15TU" was isolated which encoded a portion of the 27TU sequence (approximately amino acids 289-607 of SEQ ID NO:12). Clone 15TU was deposited with the American Type Culture Collection on June 7, 1995 and given the accession number ATCC 69847. 15TU comprises the same nucleotide sequence as 27TU over this region of amino acids.

30 A full-length clone corresponding to clone 27TU was also isolated and identified as "clone 57TU4A". The nucleotide sequence of clone 57TU4A is reported as SEQ ID NO:15. Nucleotides 336 to 5092 of SEQ ID NO:15 encode a



TNF-R1-DD ligand protein, the amino acid sequence of which is reported as SEQ ID NO:146. Amino acids 982 to 1588 of SEQ ID NO:16 correspond to amino acids 1 to 607 of SEQ ID NO:12 (clone 27TU). Clone 57TU4A was deposited with the American Type Culture Collection on February 13, 1996 and given the accession number ATCC 69988.

A full-length clone corresponding to clone 1TU was also isolated and identified as "clone 33-1B". The nucleotide sequence of clone 33-1B is reported as SEQ ID NO:17. Nucleotides 14 to 2404 of SEQ ID NO:17 encode a TNF-R1-DD ligand protein, the amino acid sequence of which is reported as SEQ ID NO:18. Amino acids 488 to 797 of SEQ ID NO:18 correspond to amino acids 1 to 310 of SEQ ID NO:10 (clone 1TU). Clone 33-1B was deposited with the American Type Culture Collection on August 13, 1996 and given the accession number ATCC 98137.

Polynucleotides hybridizing to the polynucleotides of the present invention under stringent conditions and highly stringent conditions are also part of the present invention. As used herein, "highly stringent conditions" include, for example, 0.2xSSC at 65°C; and "stringent conditions" include, for example, 4xSSC at 65°C or 50% formamide and 4xSSC at 42°C.

For the purposes of the present application, "TNF-R1-DD ligand protein" includes proteins which exhibit TNF-R1-DD ligand protein activity. For the purposes of the present application, a protein is defined as having "TNF-R1-DD ligand protein activity" when it binds to a protein derived from the TNF-R death domain. Activity can be measured by using any assay which will detect binding to an TNF-R death domain protein. Examples of such assays include without limitation the interaction trap assays and assays in which TNF-R death domain protein which is affixed to a surface in a manner conducive to observing binding, including without limitation those described in Examples 1 and 3. As used herein an "TNF-R death domain protein" includes the entire death domain or fragments thereof.

Fragments of the TNF-R1-DD ligand protein which are capable of interacting with the TNF-R death domain or which are capable of inhibiting TNF-R death domain binding (i.e., exhibit TNF-R1-DD ligand protein activity) are also

encompassed by the present invention. Fragments of the TNF-R1-DD ligand protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of TNF-R1-DD ligand protein binding sites. For example, fragments of the TNF-R1-DD ligand protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the TNF-R1-DD ligand protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, an TNF-R1-DD ligand protein - IgM fusion would generate a decavalent form of the TNF-R1-DD ligand protein of the invention.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the TNF-R1-DD ligand protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and the expression control sequence are situated within a vector or cell in such a way that the TNF-R1-DD ligand protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the TNF-R1-DD ligand protein. Host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

The TNF-R1-DD ligand protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference.

Alternatively, it may be possible to produce the TNF-R1-DD ligand protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the TNF-R1-DD ligand protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional TNF-R1-DD ligand protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The TNF-R1-DD ligand protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the TNF-R1-DD ligand protein.

The TNF-R1-DD ligand protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the TNF-R1-DD ligand protein may also include an affinity column containing the TNF-R death domain or other TNF-R death domain protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl®

or Cibacrom blue 3GA Sepharose<sup>®</sup>; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the TNF-R1-DD ligand protein of the invention may  
5 also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP) or glutathione-S-transferase (GST). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA) and Pharmacia (Piscataway, NJ), respectively. The TNF-R ligand protein can  
10 also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g.,  
15 silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the TNF-R1-DD ligand protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The TNF-R1-DD ligand protein thus purified is substantially free of other mammalian proteins and is defined  
20 in accordance with the present invention as an "isolated TNF-R1-DD ligand protein."

TNF-R1-DD ligand proteins may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The  
25 synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with TNF-R1-DD ligand proteins may possess biological properties in common therewith, including TNF-R1-DD ligand protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified TNF-R1-DD ligand proteins in  
30 screening of therapeutic compounds and in immunological processes for the development of antibodies.

The TNF-R1-DD ligand proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified TNF-R1-DD ligand proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the TNF-R1-DD ligand protein sequences may include the replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Mutagenic techniques for such replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584).

Other fragments and derivatives of the sequences of TNF-R1-DD ligand proteins which would be expected to retain TNF-R1-DD ligand protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

TNF-R1-DD ligand protein of the invention may also be used to screen for agents which are capable of inhibiting or blocking binding of an TNF-R1-DD ligand protein to the death domain of TNF-R, and thus may act as inhibitors of TNF-R death domain binding and/or TNF activity. Binding assays using a desired binding protein, immobilized or not, are well known in the art and may be used for this purpose using the TNF-R1-DD ligand protein of the invention. Examples 1 and 3 describe examples of such assays. Appropriate screening assays may be cell-based or cell-free. Alternatively, purified protein based screening assays may be used to identify such agents. For example, TNF-R1-DD ligand protein may be immobilized in purified form on a carrier and binding to purified TNF-R death domain may be measured in the presence and in the absence of potential inhibiting agents. A suitable binding assay may alternatively employ purified TNF-R death domain immobilized on a carrier, with a soluble form of a TNF-R1-DD ligand protein of the invention. Any TNF-R1-DD ligand protein may be used in the screening assays described above.

In such a screening assay, a first binding mixture is formed by combining TNF-R death domain protein and TNF-R1-DD ligand protein, and the amount of binding in the first binding mixture ( $B_0$ ) is measured. A second binding mixture is also formed by combining TNF-R death domain protein, TNF-R1-DD ligand protein, and the compound or agent to be screened, and the amount of binding in the second binding mixture ( $B$ ) is measured. The amounts of binding in the first and second binding mixtures are compared, for example, by performing a  $B/B_0$  calculation. A compound or agent is considered to be capable of inhibiting TNF-R death domain binding if a decrease in binding in the second binding mixture as compared to the first binding mixture is observed. The formulation and optimization of binding mixtures is within the level of skill in the art. Such binding mixtures may also contain buffers and salts necessary to enhance or to optimize binding, and additional control assays may be included in the screening assay of the invention.

Alternatively, appropriate screening assays may be cell based. For example, the binding or interaction between an TNF-R ligand protein and the TNF-R death domain can be measured in yeast as described below in Examples 1 and 3.

Compounds found to reduce, preferably by at least about 10%, more preferably greater than about 50% or more, the binding activity of TNF-R1-DD ligand protein to TNF-R death domain may thus be identified and then secondarily screened in other binding assays, including *in vivo* assays. By these means compounds having inhibitory activity for TNF-R death domain binding which may be suitable as anti-inflammatory agents may be identified.

Isolated TNF-R1-DD ligand protein may be useful in treating, preventing or ameliorating inflammatory conditions and other conditions, such as cachexia, autoimmune disease, graft versus host reaction, osteoporosis, colitis, myelogenous leukemia, diabetes, wasting, and atherosclerosis. Isolated TNF-R1-DD ligand protein may be used itself as an inhibitor of TNF-R death domain binding or to design inhibitors of TNF-R death domain binding. Inhibitors of binding of TNF-R1-DD ligand protein to the TNF-R death domain ("TNF-R intracellular binding inhibitors") are also useful for treating such conditions.

The present invention encompasses both pharmaceutical compositions and therapeutic methods of treatment or use which employ isolated TNF-R1-DD ligand protein and/or binding inhibitors of TNF-R intracellular binding.

Isolated TNF-R1-DD ligand protein or binding inhibitors (from  
5 whatever source derived, including without limitation from recombinant and non-recombinant cell lines) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to TNF-R1-DD ligand protein or binding inhibitor and a carrier)  
10 diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF,  
15 TNF, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, G-CSF, Meg-CSF, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other anti-inflammatory agents. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with isolated TNF-R1-DD ligand protein or binding inhibitor, or to minimize side effects  
20 caused by the isolated TNF-R1-DD ligand protein or binding inhibitor. Conversely, isolated TNF-R1-DD ligand protein or binding inhibitor may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or  
25 anti-thrombotic factor, or anti-inflammatory agent.

The pharmaceutical composition of the invention may be in the form of a liposome in which isolated TNF-R1-DD ligand protein or binding inhibitor is combined, in addition to other pharmaceutically acceptable carriers, with  
30 amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile

acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

5           As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of an inflammatory response or condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When  
10       applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

          In practicing the method of treatment or use of the present invention,  
15       a therapeutically effective amount of isolated TNF-R1-DD ligand protein or binding inhibitor is administered to a mammal having a condition to be treated. Isolated TNF-R1-DD ligand protein or binding inhibitor may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors.  
20       When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, isolated TNF-R1-DD ligand protein or binding inhibitor may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate  
25       sequence of administering isolated TNF-R1-DD ligand protein or binding inhibitor in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

          Administration of isolated TNF-R1-DD ligand protein or binding inhibitor used in the pharmaceutical composition or to practice the method of the  
30       present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, or cutaneous, subcutaneous, or intravenous injection. Intravenous administration to the patient is preferred.



When a therapeutically effective amount of isolated TNF-R1-DD ligand protein or binding inhibitor is administered orally, isolated TNF-R1-DD ligand protein or binding inhibitor will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% isolated TNF-R1-DD ligand protein or binding inhibitor, and preferably from about 25 to 90% isolated TNF-R1-DD ligand protein or binding inhibitor. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of isolated TNF-R1-DD ligand protein or binding inhibitor, and preferably from about 1 to 50% isolated TNF-R1-DD ligand protein or binding inhibitor.

When a therapeutically effective amount of isolated TNF-R1-DD ligand protein or binding inhibitor is administered by intravenous, cutaneous or subcutaneous injection, isolated TNF-R1-DD ligand protein or binding inhibitor will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to isolated TNF-R1-DD ligand protein or binding inhibitor, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of isolated TNF-R1-DD ligand protein or binding inhibitor in the pharmaceutical composition of the present invention will depend

upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of isolated TNF-R1-DD ligand protein or binding inhibitor with which to treat each individual patient. Initially, the attending physician will administer low doses of isolated TNF-R1-DD ligand protein or binding inhibitor and observe the patient's response. Larger doses of isolated TNF-R1-DD ligand protein or binding inhibitor may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.1  $\mu$ g to about 100 mg of isolated TNF-R1-DD ligand protein or binding inhibitor per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the isolated TNF-R1-DD ligand protein or binding inhibitor will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Isolated TNF-R1-DD ligand protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the TNF-R1-DD ligand protein and which may inhibit TNF-R death domain binding. Such antibodies may be obtained using either the entire TNF-R1-DD ligand protein or fragments of TNF-R1-DD ligand protein as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987).

Monoclonal antibodies binding to TNF-R1-DD ligand protein or to complex carbohydrate moieties characteristic of the TNF-R1-DD ligand glycoprotein may be useful diagnostic agents for the immunodetection of TNF-R ligand protein.

Neutralizing monoclonal antibodies binding to TNF-R1-DD ligand protein or to complex carbohydrates characteristic of TNF-R1-DD ligand glycoprotein may also be useful therapeutics for both inflammatory conditions and also in the treatment of some forms of cancer where abnormal expression of TNF-R1-DD ligand protein is involved. These neutralizing monoclonal antibodies are capable of blocking the signaling function of the TNF-R1-DD ligand protein. By blocking the binding of TNF-R1-DD ligand protein, certain biological responses to TNF are either abolished or markedly reduced. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against TNF-R1-DD ligand protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the TNF-R1-DD ligand protein.

Due to the similarity of their sequences to the insulin growth factor binding protein ("IGFBP-5") and fragments thereof which bind to the TNF-R death domain are proteins having TNF-R1-DD ligand protein activity as defined herein. As a result, they are also useful in pharmaceutical compositions, for treating inflammatory conditions and for inhibiting TNF-R death domain binding as described above for TNF-R1-DD ligand proteins generally.

#### **EXAMPLE 1** **CLONING OF TNF-R DEATH DOMAIN LIGAND** **PROTEIN ENCODING POLYNUCLEOTIDE**

A yeast genetic selection method, the "interaction trap" [Gyuris et al, Cell 75:791-803, 1993, which is incorporated herein by reference], was used to screen WI38 cell cDNA libraries (preparation, see below) for proteins that interact with the death domain of the P55 type 1 TNF receptor (TNF-R1-DD). A polynucleotide encoding amino acids 326 to 413 of the P55 type TNF receptor, TNF-R1-DD, was obtained via the polymerase chain reaction (PCR) using a grafting method. This TNF-R1-DD DNA was then cloned into pEG202 by BamHI and Sall sites, generating the bait plasmid, pEG202-TNF-R1-DD. This plasmid contains the

HIS3 selectable marker, and expression of the bait, the LexA-TNF-R1-DD fusion protein, is from the strong constitutive ADH1 promoter. To create the reporter strain carrying the bait protein, yeast strain EGY48, containing the reporter sequence LexAop-Leu2 in place of the chromosomal LEU2, was transformed with  
5 pEG202-TNF-R1-DD and pSH18-34 (Ura+), which carries another reporter sequence, LexAop-lacZ. For screening cDNAs encoding proteins that interact with TNF-R1-DD, the expression vector pJG4-5 (TRP1), containing the WI38 cell cDNA library (see below for the cDNA library construction), was transformed into the above strain (EGY48/pEG202-TNF-R1-DD/pSH18-34) according to the method  
10 described by Gietz *et al.*, Nucleic Acids Res., 20:1425 (1992).

#### cDNA Library Construction:

WI38 cell cDNA library: Double stranded cDNA was prepared from 3ug of WI38 mRNA using reagents provided by the Superscript Choice System  
15 (Gibco/BRL, Gaithersburg, MD) with the following substitutions: the first strand synthesis was primed using an oligo dT/XhoI primer/linker, and the dNTP mix was substituted with a mix containing methyl dCTP (Stratagene, LaJolla, CA). The cDNA was modified at both ends by addition of an EcoRI/NotI/SalI adapter linker and subsequently digested with XhoI. This produced cDNA molecules possessing  
20 an EcoRI/NotI/SalI overhang at the 5' end of the gene and an XhoI overhang at the 3' end. These fragments were then ligated into the yeast expression/fusion vector pJG4-5 (Gyuris *et al.*, Cell, 75, 791-803, 1993), which contains at its amino terminus, the influenza virus HA1 epitope tag, the B42 acidic transcription activation domain, and the SV40 nuclear localization signal, all under the control  
25 of the galactose-dependent GAL1 promoter. The resulting plasmids were then electroporated into DH10B cells (Gibco/BRL). A total of  $7.1 \times 10^6$  colonies were plated on LB plates containing 100 ug/ml of ampicillin. These *E. coli* were scraped, pooled, and a large scale plasmid prep was performed using the Wizard Maxi Prep kit (Promega, Madison, WI), yielding 3.2mg of supercoiled plasmid DNA.

30

#### WI38 Cell cDNA Screening Results:

1 x 10<sup>6</sup> transformants were obtained on glucose Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup> plates. These transformants were pooled and resuspended in a solution of 65% glycerol, 10mM Tris-HCl (pH 7.5), 10 mM MgCl<sub>2</sub> and stored at -80°C in 1mL aliquots. For screening purposes, aliquots of these were diluted 10-fold into Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup> CM dropout gal/raff medium (containing 2% galactose, 1% raffinose), which induces the expression of the library encoded proteins, and incubated at 30°C for 4 hours. 12 x 10<sup>6</sup> colony forming units (CFUs) were then plated on standard 10cm galactose X-Gal Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup>Leu<sup>-</sup> plates at a density of 2 x 10<sup>5</sup> CFU/plate. After three days at 30°C, about 1,000 colonies were formed (Leu<sup>+</sup>) and of those, sixty-four colonies were LacZ<sup>+</sup>. In order to test if the Leu<sup>+</sup>/LacZ<sup>+</sup> phenotype was due to the library-encoded protein, the galactose dependency of the phenotype was tested. Expression of the library-encoded proteins was turned off by growth on glucose Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup> master plates and then retested for galactose-dependency on glucose Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup>Leu<sup>-</sup>, galactose Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup>Leu<sup>-</sup>, glucose X-Gal Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup>, and galactose X-Gal Ura<sup>-</sup>His<sup>-</sup>Trp<sup>-</sup> plates. Of these, 32 colonies showed galactose-dependent growth on Leu<sup>-</sup> plates and galactose-dependent blue color on X-Gal-containing medium (LacZ<sup>+</sup> phenotype). Total yeast DNA was prepared from these colonies according to the method described previously (Hoffman and Winston, 1987). In order to analyze the cDNA sequences, PCR reactions were performed using the above yeast DNA as a template and oligo primers specific for the vector pJG4-5, flanking the cDNA insertion point. PCR products were purified (Qiagen PCR purification kit), subjected to restriction digest with the enzyme HaeIII, run on 1.8% agarose gels, and the restriction patterns compared. Similar and identical restriction patterns were grouped and representatives of each group were sequenced and compared to Genbank and other databases to identify any sequence homologies.

One clone of unique sequence ("2DD") and three clones with identical sequence ("3DD") were isolated and showed no significant sequence homologies compared to Genbank and other databases. Additionally, four other clones ("20DD") with identical sequence to a portion of human insulin-like growth factor binding protein-5 (Shunichi Shimasaki *et al.*, J. Biol. Chem. 266:10646-10653 (1991)) were isolated. The clones "2DD," "3DD" and "20DD" were chosen for further analysis. Library vector pJG4-5 containing these clones sequences were

rescued from yeast by transforming the total yeast DNAs into the *E. coli* strain KC8 and selecting for growth on Trp-ampicillin plates. These putative TNFR1 interacting proteins were then tested further for specificity of interaction with the TNF-R1-DD by the reintroduction of JG4-5 clone into EGY48 derivatives containing a panel of different baits, including bicoid, the cytoplasmic domain of the IL-1 receptor, and TNF-R1-DD. The above clones were found to interact only with the TNF-R1-DD. The interaction between these clones and TNF-R1-DD was thus judged to be specific.

#### 10      U937 cDNA Screening Results:

A U937 cDNA library was also constructed and screened as described above. 1,020 Leu<sup>+</sup> colonies were found and of those, 326 colonies were also LacZ<sup>+</sup>. 62 colonies of these Leu<sup>+</sup>/LacZ<sup>+</sup> colonies showed a galactose-dependent phenotype. One of these clones, 1TU, encodes a novel sequence. Interestingly, two clones, 15TU and 27TU, encode related or identical sequences, except that 27TU contains about 864 additional nucleotides (or about 288 amino acids) at the 5' end. 15/27TU also encode a novel sequence.

#### 20      EXAMPLE 2 EXPRESSION OF THE TNF-R1-DD ligand PROTEIN

cDNAs encoding TNF-R intracellular ligand proteins were released from the pJG4-5 vector with the appropriate restriction enzymes. For example, EcoRI and XhoI or NotI and XhoI were used to release cDNA from clone 2DD and clone 20DD. Where the restriction sites were also present in the internal sequence of the cDNA, PCR was performed to obtain the cDNA. For example, the cDNA fragment encoding "clone 3DD" was obtained through PCR due to the presence of an internal XhoI site. These cDNAs were then cloned into various expression vectors. These included pGEX (Pharmacia) or pMAL (New England Biolabs) for expression as a GST (Glutathione-S-transferase) or MBP (maltose binding protein) fusion protein in *E. coli*, a pED-based vector for mammalian expression, and pVL or pBlueBacHis (Invitrogen) for baculovirus/insect expression. For the immunodetection of TNF-R intracellular ligand expression in mammalian cells, an

epitope sequence, "Flag," was inserted into the translational start site of the pED vector, generating the pED-Flag vector. cDNAs were then inserted into the pED-Flag vector. Thus, the expression of cDNA from pED-Flag yields a protein with an amino terminal Met, followed by the "Flag" sequence, Asp-Tyr-Lys-Asp-Asp-Asp-Lys. Standard DEAE-Dextran or lipofectamine methods were used to transfect COS or CHO dukx cells. Immunodetection of Flag-tagged proteins was achieved using the M2 antibody (Kodak). Moreover, an immunoaffinity column using the M2 antibody, followed by elution with the "Flag" peptide, can be used for the rapid purification of the flag-tagged protein. Similarly, affinity purification of GST-, MBP- or His-tagged fusion proteins can be performed using glutathione, amylose, or nickel columns. Detailed purification protocols are provided by the manufacturers. For many fusion proteins, the TNF-R intracellular ligand can be released by the action of thrombin, factor Xa, or enterokinase cleavage. In the case where highly purified material is required, standard purification procedures, such as ion-exchange, hydrophobic, and gel filtration chromatography will be applied in addition to the affinity purification step.

Figs. 1 and 2 depict autoradiographs demonstrating the expression of TNF-R1-DD ligand proteins in yeast and mammalian cells. Fig. 1 shows the results of expression of isolated clones of the present invention in yeast. EGY48 was transformed with pJG4-5 containing clone 2DD, 3DD or 20DD. Cells were then grown overnight in the galactose/raffinose medium. Cell lysates were prepared and subject to 4-20% SDS gel electrophoresis, followed by Western blot analysis using anti-HA antibody (12CA5, Boehringer Mannheim, Indianapolis, IN). Fig. 2 shows the results of expression of Flag-2DD and Flag-20DD in COS cells. COS cells were transfected with either pED-Flag (Vector control), Flag-2DD or Flag-20DD plasmid by the lipofectamine method. Thirty  $\mu$ g of each cell lysate were prepared and subjected to 4-20% SDS gel electrophoresis, followed by Western blot analysis using M2 antibody (Kodak). The bands in the Flag-2DD and Flag-20DD lanes indicate significant expression of the respective TNF-R1-DD ligand proteins.

### **EXAMPLE 3**

#### **ASSAYS OF TNF-R DEATH DOMAIN BINDING**

Two different methods were used to assay for TNF-R1-DD ligand protein activity. The first assay measures binding in the yeast strain in "interaction trap," the system used here to screen for TNF-R1-DD interacting proteins. In this system, the expression of reporter genes from both LexAop-Leu2 and LexAop-LacZ relies on the interaction between the bait protein, in this case TNF-R1DD, and the prey, the TNF-R intracellular ligand. Thus, one can measure the strength of the interaction by the level of Leu2 or LacZ expression. The most simple method is to measure the activity of the LacZ encoded protein,  $\beta$ -galactosidase. This activity can be judged by the degree of blueness on the X-Gal containing medium or filter. For the quantitative measurement of  $\beta$ -galactosidase activity, standard assays can be found in "Methods in Yeast Genetics" Cold Spring Harbor, New York, 1990 (by Rose, M.D., Winston, F., and Hieter, P.).

The second assay for measuring binding is a cell-free system. An example of a typical assay is described below. Purified GST-TNF-R1-DD fusion protein (2 ug) was mixed with amylose resins bound with a GST-TNF-R1-DD intracellular ligand for 2 hour at 4°C. The mixture was then centrifuged to separate bound (remained with the beads) and unbound (remained in the supernatant) GST-TNF-R1-DD. After extensive washing, the bound GST-TNF-R1-DD was eluted with maltose and detected by Western blot analysis using a GST antibody. The TNF-R1-DD or the intracellular ligand can also be immobilized on other solid supports, such as on plates or fluorobeads. The binding can then be measured using ELISA or SPA (scintillation proximity assay).

### **EXAMPLE 4**

#### **CHARACTERIZATION OF TNF-R**

#### **DEATH DOMAIN LIGAND PROTEIN**

##### **Mapping the interaction site in TNF-R1**

Many of the key amino acids for TNF-R signaling have been determined by site-directed mutagenesis (Tataglia *et al.*, Cell 74:845-853 (1993)). These amino acids are conserved between TNF-R and the Fas antigen, which is



required for mediating cytotoxicity and other cellular responses. In order to test if the TNF-R intracellular proteins interact with these residues, the following mutations were constructed: F345A (substitution of phe at amino acid 345 to Ala), R347A, L351A, F345A/R347A/L351A, E369A, W378A and I408A. The ability of the mutant protein to interact with the intracellular ligand in the "interaction trap" system was tested.

#### Effect on the TNF-mediated response

The effect of the TNF-R intracellular ligands on the TNF-mediated response can be evaluated in cells overexpressing the ligands. A number of TNF-mediated responses, including transient or prolonged responses, can be measured. For example, TNF-induced kinase activity toward either MBP (myelin basic protein) or the N-terminus (amino acids 1-79) of c-jun can be measured in COS cells or CHO cells either transiently or stably overexpressing clone 2DD, 3DD or clone 20DD. The significance of these ligand proteins in TNF-mediated cytotoxicity and other cellular responses can be measured in L929 or U937 overexpressing cells. Alternatively, other functional assays, such as the induction of gene expression or PGE<sub>2</sub> production after prolonged incubation with TNF, can also be used to measure the TNF mediated response. Conversely, the significance of the TNF-R1-DD ligand proteins in TNF signaling can be established by lowering or eliminating the expression of the ligands. These experiments can be performed using antisense expression or transgenic mice.

#### Enzymatic or functional assays

The signal transduction events initiated by TNF binding to its receptor are still largely unknown. However, one major result of TNF binding is the stimulation of cellular serine/threonine kinase activity. In addition, TNF has been shown to stimulate the activity of PC-PLC, PLA<sub>2</sub>, and sphingomyelinase. Therefore, some of the TNF-R1-DD ligand proteins may possess intrinsic enzymatic activity that is responsible for these activities. Therefore, enzymatic assays can be performed to test this possibility, particularly with those clones that encode proteins with sequence homology to known enzymes. In addition to enzymatic activity, based on

the sequence homology to proteins with known function, other functional assays can also be measured.

#### EXAMPLE 5 ISOLATION OF FULL LENGTH CLONES

In many cases, cDNAs obtained from the interaction trap method each encode only a portion of the full length protein. For example, based on identity and sequence and the lack of the initiating methionine codon, clones 2DD, 3DD and 20DD apparently do not encode full length proteins. Therefore, it is desirable to isolate full length clones. The cDNAs obtained from the screening, such as clone 2DD, are used as probes, and the cDNA libraries described herein, or alternatively phage cDNA libraries, are screened to obtain full length clones in accordance with known methods (see for example, "Molecular Cloning, A Laboratory Manual", by Sambrook et al., 1989 Cold Spring Harbor).

#### EXAMPLE 6 ANTIBODIES SPECIFIC FOR TNF-R INTRACELLULAR LIGAND PROTEIN

Antibodies specific for TNF-R intracellular ligand proteins can be produced using purified recombinant protein, as described in Example 2, as antigen. Both polyclonal and monoclonal antibodies will be produced using standard techniques, such as those described in "Antibodies, a Laboratory Manual" by Ed Harlow and David Lane (1988), Cold Spring Harbor Laboratory.

#### EXAMPLE 7 CHARACTERIZATION OF CLONES 1TU AND 15/27TU

##### Specificity of Interaction

The specificity of clones 1TU, 15TU and 27TU was tested using a panel of baits. The ability of these clones to bind the TNF-R death domain was compared to their binding to the intracellular domain of the second TNF-R (TNF-R p75<sub>IC</sub>), the entire intracellular domain of TNF-R (TNF-R p55<sub>IC</sub>), the death domain of the fas antigen (which shares 28% identity with TNF-R-DD) (Fas<sub>DD</sub>), the *Drosophila*

transcription factor bicoid, and a region of the IL-1 receptor known to be critical for signalling (IL-1R<sub>477-527</sub>). As shown in Table 1, none of these clones interacted with TNF-R p75<sub>IC</sub> or Fas<sub>DD</sub>, and only 1TU interacted with bicoid. In contrast, both 1TU and 15TU bound the cytoplasmic domain of the p55 TNF-R, as well as residues 477-527 of the IL-1R. 27TU interacted relatively weakly with these sequences.

Table 1

clone	TNF-R <sub>DD</sub>	TNF-R p75 <sub>IC</sub>	TNF-R p55 <sub>IC</sub>	Fas <sub>DD</sub>	bicoid	IL-1R (477-527)
1TU	+++	-	+++	-	++	+++
15TU	+++	±	+++	-	-	++
27TU	+++	-	+	-	-	+

#### Interaction with Amino Acids Critical for Signalling

The ability of each clone to interact with four single-site mutations in the TNF-R death domain (each known to abolish signalling) was measured. As shown in Table 2, each of the clones interacted less strongly with the death domain mutants than with the wild type death domain, suggesting that these clones may bind critical residues *in vivo*.

Table 2

clone	TNF-R <sub>DD</sub>	F345A	L351A	W378A	I408A
1TU	+++	+	++	++	+
15TU	+++	+	+	++	++
27TU	+++	+	+	±	++

#### Expression of 1TU, 15TU and 27TU

Fig. 3 depicts an autoradiograph demonstrating the expression of clones 1TU, 15TU and 27TU in yeast (A) and COS cells (B).

In (A): EGY48 was transformed with pJG4-5 containing clones 1TU, 15TU or 27TU. Cells were then grown overnight in galactose/raffinose medium. Cell lysates were prepared and subjected to 4-20% SDS gel electrophoresis, followed by Western blot analysis using anti-HA antibody (12CA5, Boehringer Mannheim).

In (B): COS cells were transfected with pED-Flag containing clones 1TU, 15TU and 27TU. Cell lysates were prepared and analyzed by Western blot using anti-Flag antibody (M2, Kodak).

#### 10 Specific Binding of 1TU and 27TU to TNF-R1-DD

The interaction of 1TU and 27TU with TNF-R1-DD was tested using purified bacterially expressed fusion proteins. As shown in Fig. 4, MBP fusion proteins containing 1TU or 27TU bound only to TNF-R1-DD expressed as a GST fusion protein, but not to GST protein alone. In the control experiment, MBP protein did not bind either GST or GST/TNF-R1-DD. These results indicate that 15 1TU and 27TU bound specifically to the TNF-R1 death domain *in vitro*, confirming the data obtained in the interaction trap.

#### 20 15TU and 27TU Activation of JNK Activity

The jun N-terminal kinase (JNK) is normally activated within 15 min of TNF treatment in COS cells. 15TU and 27TU were cotransfected with an epitope tagged version of JNK, HA-JNK, in duplicate. After TNF treatment, JNK was immunoprecipitated with anti-HA antibody and JNK activity was measured in immunoprecipitation kinase assays, using GST-c-jun (amino acids 1-79) as 25 substrate). Reactions were electrophoresed on SDS-PAGE. As shown in Fig. 5, transfection of 15TU and 27TU, but not vector alone, into COS cells activated JNK even in the absence of TNF, suggesting that these clones are involved in signal transduction of TNF and the pathway leading to JNK activation *in vivo*.

30

### EXAMPLE 8 ISOLATION, EXPRESSION AND ASSAY OF CLONE 3TW

Clone 3TW was isolated from the WI38 cDNA library using clone 3DD as a probe. Clone 3TW was expressed. Fig. 6 is an autoradiograph which demonstrates expression of 3TW (indicated by arrow).

- An antisense oligonucleotide was derived from the sequence of clone 3TW.
- 5 The antisense oligonucleotide was assayed to determine its ability to inhibit TNF-induced cPLA<sub>2</sub> phosphorylation. Fig. 7 depicts the results of that experiment. Activity of the antisense oligonucleotide (3TWAS) was compared with the full-length clone (3TWFL), Flag-3TW full length (3TWFLflag) and pED-flag vector (pEDflag). The antisense oligonucleotide inhibited phosphorylation.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANT: Lin, Lih-Ling  
Chen, Jennifer H.  
Schievella, Andrea  
Graham, James
- (ii) TITLE OF INVENTION: NOVEL TNF RECEPTOR DEATH DOMAIN LIGAND  
PROTEINS AND INHIBITORS OF LIGAND BINDING
- (iii) NUMBER OF SEQUENCES: 18
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: Genetics Institute, Inc.
  - (B) STREET: 87 CambridgePark Drive
  - (C) CITY: Cambridge
  - (D) STATE: Massachusetts
  - (E) COUNTRY: USA
  - (F) ZIP: 02140
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Floppy disk
  - (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER:
  - (B) FILING DATE:
  - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Brown, Scott A,
  - (B) REGISTRATION NUMBER: 32,724
  - (C) REFERENCE/DOCKET NUMBER: GI5232D
- (ix) TELECOMMUNICATION INFORMATION:
  - (A) TELEPHONE: (617) 498-8224
  - (B) TELEFAX: (617) 876-5851

## (2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2158 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (iii) HYPOTHETICAL: NO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 2..1231
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

C AGC AAT GCA GGT GAT GGA CCA GGT GGC GAG GGC AGT GTT CAC CTG  
 Ser Asn Ala Gly Asp Gly Pro Gly Gly Glu Gly Ser Val His Leu  
 1 5 10 15

46

GCA AGC TCT CGG GGC ACT TTG TCT GAT AGT GAA ATT GAG ACC AAC TCT	94
Ala Ser Ser Arg Gly Thr Leu Ser Asp Ser Glu Ile Glu Thr Asn Ser	
20 25 30	
GCC ACA AGC ACC ATC TTT GGT AAA GCC CAC AGC TTG AAG CCA AGC ATA	142
Ala Thr Ser Thr Ile Phe Gly Lys Ala His Ser Leu Lys Pro Ser Ile	
35 40 45	
AAG GAG AAG CTG GCA GGC AGC CCC ATT CGT ACT TCT GAA GAT GTG AGC	190
Lys Glu Lys Leu Ala Gly Ser Pro Ile Arg Thr Ser Glu Asp Val Ser	
50 55 60	
CAG CGA GTC TAT CTC TAT GAG GGA CTC CTA GGC AAA GAG CGT TCT ACT	238
Gln Arg Val Tyr Leu Tyr Glu Gly Leu Leu Gly Lys Glu Arg Ser Thr	
65 70 75	
TTA TGG GAC CAA ATG CAA TTC TGG GAA GAT GCC TTC TTA GAT GCT GTG	286
Leu Trp Asp Gln Met Phe Trp Glu Asp Ala Phe Leu Asp Ala Val	
80 85 90 95	
ATG TTG GAG AGA GAA GGG ATG GGT ATG GAC CAG GGT CCC CAG GAA ATG	334
Met Leu Glu Arg Glu Gly Met Gly Met Asp Gln Gly Pro Gln Glu Met	
100 105 110	
ATC GAC AGG TAC CTG TCC CTT GGA GAA CAT GAC CGG AAG CGC CTG GAA	382
Ile Asp Arg Tyr Leu Ser Leu Gly Glu His Asp Arg Lys Arg Leu Glu	
115 120 125	
GAT GAT GAA GAT CGC TTG CTG GCC ACA CTT CTG CAC AAC CTC ATC TCC	430
Asp Asp Glu Asp Arg Leu Leu Ala Thr Leu Leu His Asn Leu Ile Ser	
130 135 140	
TAC ATG CTG CTG ATG AAG GTA AAT AAG AAT GAC ATC CGC AAG AAG GTG	478
Tyr Met Leu Leu Met Lys Val Asn Lys Asn Asp Ile Arg Lys Lys Val	
145 150 155	
AGG CGC CTA ATG GGA AAG TCG CAC ATT GGG CTT GTG TAC AGC CAG CAA	526
Arg Arg Leu Met Gly Lys Ser His Ile Gly Leu Val Tyr Ser Gln Gln	
160 165 170 175	
ATC AAT GAG GTG CTT GAT CAG CTG GCG AAC CTG AAT GGA CGC GAT CTC	574
Ile Asn Glu Val Leu Asp Gln Leu Ala Asn Leu Asn Gly Arg Asp Leu	
180 185 190	
TCT ATC TGG TCC AGT GGC AGC CGG CAC ATG AAG AAG CAG ACA TTT GTG	622
Ser Ile Trp Ser Ser Gly Ser Arg His Met Lys Lys Gln Thr Phe Val	
195 200 205	
GTA CAT GCA GGG ACA GAT ACA AAC GGA GAT ATC TTT TTC ATG GAG GTG	670
Val His Ala Gly Thr Asp Thr Asn Gly Asp Ile Phe Phe Met Glu Val	
210 215 220	
TGC GAT GAC TGT GTG GTG TTG CGT AGT AAC ATC GGA ACA GTG TAT GAG	718
Cys Asp Asp Cys Val Val Leu Arg Ser Asn Ile Gly Thr Val Tyr Glu	
225 230 235	
CGC TGG TGG TAC GAG AAG CTC ATC AAC ATG ACC TAC TGT CCC AAG ACG	766
Arg Trp Trp Tyr Glu Lys Leu Ile Asn Met Thr Tyr Cys Pro Lys Thr	
240 245 250 255	
AAG GTG TTG TGC TTG TGG CGT AGA AAT GGC TCT GAG ACC CAG CTC AAC	814
Lys Val Leu Cys Leu Trp Arg Arg Asn Gly Ser Glu Thr Gln Leu Asn	
260 265 270	

AAG TTC TAT ACT AAA AAG TGT CGG GAG CTG TAC TAC TGT GTG AAG GAC Lys Phe Tyr Thr Lys Lys Cys Arg Glu Leu Tyr Tyr Cys Val Lys Asp 275 280 285	862
AGC ATG GAG CGC GCT GCC GCC CGA CAG CAA AGC ATC AAA CCC GGA CCT Ser Met Glu Arg Ala Ala Ala Arg Gln Gln Ser Ile Lys Pro Gly Pro 290 295 300	910
GAA TTG GGT GGC GAG TTC CCT GTG CAG GAC CTG AAG ACT GGT GAG GGT Glu Leu Gly Gly Glu Phe Pro Val Gln Asp Leu Lys Thr Gly Glu Gly 305 310 315	958
GGC CTG CTG CAG GTG ACC CTG GAA GGG ATC AAC CTC AAA TTC ATG CAC Gly Leu Leu Gln Val Thr Leu Glu Gly Ile Asn Leu Lys Phe Met His 320 325 330 335	1006
AAT CAG GTT TTC ATA GAG CTG AAT CAC ATT AAA AAG TGC AAT ACA GTT Asn Gln Val Phe Ile Glu Leu Asn His Ile Lys Lys Cys Asn Thr Val 340 345 350	1054
CGA GGC GTC TTT GTC CTG GAG GAA TTT GTT CCT GAA ATT AAA GAA GTG Arg Gly Val Phe Val Leu Glu Glu Phe Val Pro Glu Ile Lys Glu Val 355 360 365	1102
GTG AGC CAC AAG TAC AAG ACA CCA ATG GCC CAC GAA ATC TGC TAC TCC Val Ser His Lys Tyr Lys Thr Pro Met Ala His Glu Ile Cys Tyr Ser 370 375 380	1150
GTA TTA TGT CTC TTC TCG TAC GTG GCT GCA GTT CAT AGC AGT GAG GAA Val Leu Cys Leu Phe Ser Tyr Val Ala Ala Val His Ser Ser Glu Glu 385 390 395	1198
GAT CTC AGA ACC CCG CCC CGG CCT GTC TCT AGC TGATGGAGAG GGGCTACGCA Asp Leu Arg Thr Pro Pro Arg Pro Val Ser Ser 400 405 410	1251
GCTGCCCCAG CCCAGGGCAC GCCCCTGGCC CCTTGCTGTT CCCAAGTGCA CGATGCTGCT	1311
GTGACTGAGG AGTGGATGAT GCTCGTGTGT CCTCTGCAAG CCCCTGCTG TGGCTTGGGT	1371
GGGTACCGGT TATGTGTCCC TCTGAGTGTG TCTTGAGCGT GTCCACCTTC TCCCTCTCCA	1431
CTCCCAGAAG ACCAAACTGC CTTCCCCCTCA GGGCTCAAGA ATGTGTACAG TCTGTGGGGC	1491
CGGTGTGAAC CCACTATTTT GTGTCCTTGA GACATTTGTG TTGTGGTTCC TTGTCCTTGT	1551
CCCTGGCGTT AACTGTCCAC TGCAAGAGTC TGGCTCTCCC TTCTCTGTGA CCCGGCATGA	1611
CTGGGCGCCT GGAGCAGTTT CACTCTGTGA GGAGTGAGGG AACCCTGGGG CTCACCCTCT	1671
CAGAGGAAGG GCACAGAGAG GAAGGGAAGA ATTGGGGGGC AGCCGGAGTG AGTGGCAGCC	1731
TCCCTGCTTC CTTCTGCATT CCCAAGCCGG CAGCTACTGC CCAGGGCCCCG CAGTGTGGC	1791
TGCTGCCTGC CACAGCCTCT GTGACTGCAG TGGAGCGGCG AATTCCCTGT GGCCTGCCAC	1851
GCCTTCGGCA TCAGAGGATG GAGTGGTCGA GGCTAGTGGA GTCCCAGGGA CCGCTGGCTG	1911
CTCTGCCTGA GCATCAGGGA GGGGGCAGGA AAGACCAAGC TGGGTTTGCA CATCTGTCTG	1971
CAGGCTGTCT CTCCAGGCAC GGGGTGTCAG GAGGGAGAGA CAGCCTGGGT ATGGGCAAGA	2031
AATGACTGTA AATATTTTTCAG CCCACATTA TTTATAGAAA ATGTACAGTT GTGTGAATGT	2091
GAAATAAATG TCCTCACCTC CCAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	2151
AAAAAAA	2158



# 2. INFORMATION FOR SEQ ID NO:2:

## (a) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 410 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(c) MOLECULE TYPE: protein

## (ix) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Ser Asn Ala Gly Asp Gly Pro Gly Gly Glu Gly Ser Val His Leu Ala
 1           5           10           15
Ser Ser Arg Gly Thr Leu Ser Asp Ser Glu Ile Glu Thr Asn Ser Ala
          20           25           30
Thr Ser Thr Ile Phe Gly Lys Ala His Ser Leu Lys Pro Ser Ile Lys
          35           40           45
Glu Lys Leu Ala Gly Ser Pro Ile Arg Thr Ser Glu Asp Val Ser Gln
          50           55           60
Arg Val Tyr Leu Tyr Glu Gly Leu Leu Gly Lys Glu Arg Ser Thr Leu
          65           70           75           80
Trp Asp Gln Met Gln Phe Trp Glu Asp Ala Phe Leu Asp Ala Val Met
          85           90           95
Leu Glu Arg Glu Gly Met Gly Met Asp Gln Gly Pro Gln Glu Met Ile
          100          105          110
Asp Arg Tyr Leu Ser Leu Gly Glu His Asp Arg Lys Arg Leu Glu Asp
          115          120          125
Asp Glu Asp Arg Leu Leu Ala Thr Leu Leu His Asn Leu Ile Ser Tyr
          130          135          140
Met Leu Leu Met Lys Val Asn Lys Asn Asp Ile Arg Lys Lys Val Arg
          145          150          155          160
Arg Leu Met Gly Lys Ser His Ile Gly Leu Val Tyr Ser Gln Gln Ile
          165          170          175
Asn Glu Val Leu Asp Gln Leu Ala Asn Leu Asn Gly Arg Asp Leu Ser
          180          185          190
Ile Trp Ser Ser Gly Ser Arg His Met Lys Lys Gln Thr Phe Val Val
          195          200          205
His Ala Gly Thr Asp Thr Asn Gly Asp Ile Phe Phe Met Glu Val Cys
          210          215          220
Asp Asp Cys Val Val Leu Arg Ser Asn Ile Gly Thr Val Tyr Glu Arg
          225          230          235          240
Trp Trp Tyr Glu Lys Leu Ile Asn Met Thr Tyr Cys Pro Lys Thr Lys
          245          250          255
Val Leu Cys Leu Trp Arg Arg Asn Gly Ser Glu Thr Gln Leu Asn Lys
          260          265          270
Phe Tyr Thr Lys Lys Cys Arg Glu Leu Tyr Tyr Cys Val Lys Asp Ser
          275          280          285

```

Met Glu Arg Ala Ala Ala Arg Gln Gln Ser Ile Lys Pro Gly Pro Glu  
 290 295 300

Leu Gly Gly Glu Phe Pro Val Gln Asp Leu Lys Thr Gly Glu Gly Gly  
 305 310 315 320

Leu Leu Gln Val Thr Leu Glu Gly Ile Asn Leu Lys Phe Met His Asn  
 325 330 335

Gln Val Phe Ile Glu Leu Asn His Ile Lys Lys Cys Asn Thr Val Arg  
 340 345 350

Gly Val Phe Val Leu Glu Glu Phe Val Pro Glu Ile Lys Glu Val Val  
 355 360 365

Ser His Lys Tyr Lys Thr Pro Met Ala His Glu Ile Cys Tyr Ser Val  
 370 375 380

Leu Cys Leu Phe Ser Tyr Val Ala Ala Val His Ser Ser Glu Glu Asp  
 385 390 395 400

Leu Arg Thr Pro Pro Arg Pro Val Ser Ser  
 405 410

## (2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 826 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

- (ix) FEATURE:  
 (A) NAME/KEY: CDS  
 (B) LOCATION: 2..415

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

G GAG GTG CAG GAC CTC TTC GAA GCC CAG GGC AAT GAC CGA CTG AAG	46
Glu Val Gln Asp Leu Phe Glu Ala Gln Gly Asn Asp Arg Leu Lys	
1 5 10 15	
CTG CTG GTG CTG TAC AGT GGA GAG GAT GAT GAG CTG CTA CAG CGG GCA	94
Leu Leu Val Leu Tyr Ser Gly Glu Asp Asp Glu Leu Leu Gln Arg Ala	
20 25 30	
GCT GCC GGG GGC TTG GCC ATG CTT ACC TCC ATG CGG CCC ACG CTC TGC	142
Ala Ala Gly Gly Leu Ala Met Leu Thr Ser Met Arg Pro Thr Leu Cys	
35 40 45	
AGC CGC ATT CCC CAA GTG ACC ACA CAC TGG CTG GAG ATC CTG CAG GCC	190
Ser Arg Ile Pro Gln Val Thr Thr His Trp Leu Glu Ile Leu Gln Ala	
50 55 60	
CTG CTT CTG AGC TCC AAC CAG GAG CTG CAG CAC CGG GGT GCT GTG GTG	238
Leu Leu Ser Ser Asn Gln Glu Leu Gln His Arg Gly Ala Val Val	
65 70 75	
GTG CTG AAC ATG GTG GAG GCC TCG AGG GAG ATT GCC AGC ACC CTG ATG	286
Val Leu Asn Met Val Glu Ala Ser Arg Glu Ile Ala Ser Thr Leu Met	
80 85 90 95	

GAG AGT GAG ATG ATG GAG ATC TTG TCA GTG CTA GCT AAG GGT GAC CAC 334  
 Glu Ser Glu Met Met Glu Ile Leu Ser Val Leu Ala Lys Gly Asp His  
 100 105 110

AGC CCT GTC ACA AGG GGT GGT GCA GGC TGC CTC GAC AAA GCA GTG GAA 382  
 Ser Pro Val Thr Arg Ala Ala Ala Ala Cys Leu Asp Lys Ala Val Glu  
 115 120 125

TAT GGG CTT ATC CAA CCC AAC CAA GAT GGA GAG TGAGGGGGTT GTCCCTGGGC 435  
 Tyr Gly Leu Ile Gln Pro Asn Gln Asp Gly Glu  
 130 135

CCAAGGCTCA TGCACACGCT ACCTATTGTG GCACGGAGAG TAAGGACGGA AGCAGCTTTG 495  
 GCTSGTGGTG GCTGGCATGC CCAATACTCT TGCCCATCCT CGCTTGCTGC CCTAGGATGT 555  
 CCTCTGTTCT GAGTCAGCGG CCACGTTTCA TACACAGCC CTGCTTGGCC AGCACTGCCT 615  
 GCAGCCTCAC TCAGAGGGGC CCTTTTCTG TACTACTGTA GTCAGCTGGG AATGGGGAAG 675  
 GTGCATCCCA ACACAGCCTG TGGATCCTGG GGCATTGGA AGGGCGCACA CATCAGCAGC 735  
 CTCACCAGCT GTGAGCCTGC TATCAGGCCT GCCCCTCCAA TAAAAGTGTG TAGAACTCCA 795  
 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA A 826

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 138 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Glu Val Gln Asp Leu Phe Glu Ala Gln Gly Asn Asp Arg Leu Lys Leu  
 1 5 10 15

Leu Val Leu Tyr Ser Gly Glu Asp Asp Glu Leu Leu Gln Arg Ala Ala  
 20 25 30

Ala Gly Gly Leu Ala Met Leu Thr Ser Met Arg Pro Thr Leu Cys Ser  
 35 40 45

Arg Ile Pro Gln Val Thr Thr His Trp Leu Glu Ile Leu Gln Ala Leu  
 50 55 60

Leu Leu Ser Ser Asn Gln Glu Leu Gln His Arg Gly Ala Val Val Val  
 65 70 75 80

Leu Asn Met Val Glu Ala Ser Arg Glu Ile Ala Ser Thr Leu Met Glu  
 85 90 95

Ser Glu Met Met Glu Ile Leu Ser Val Leu Ala Lys Gly Asp His Ser  
 100 105 110

Pro Val Thr Arg Ala Ala Ala Ala Cys Leu Asp Lys Ala Val Glu Tyr  
 115 120 125

Gly Leu Ile Gln Pro Asn Gln Asp Gly Glu  
 130 135

## (2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 722 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 2..559

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

G GAG AAG CCG CTG CAC GCC CTG CTG CAC GGC CGC GGG GTT TGC CTC	46
Glu Lys Pro Leu His Ala Leu Leu His Gly Arg Gly Val Cys Leu	
1 5 10 15	
AAC GAA AAG AGC TAC CGC GAG CAA GTC AAG ATC GAG AGA GAC TCC CGT	94
Asn Glu Lys Ser Tyr Arg Glu Gln Val Lys Ile Glu Arg Asp Ser Arg	
20 25 30	
GAG CAC GAG GAG CCC ACC ACC TCT GAG ATG GCC GAG GAG ACC TAC TCC	142
Glu His Glu Glu Pro Thr Thr Ser Glu Met Ala Glu Glu Thr Tyr Ser	
35 40 45	
CCC AAG ATC TTC CGG CCC AAA CAC ACC CGC ATC TCC GAG CTG AAG GCT	190
Pro Lys Ile Phe Arg Pro Lys His Thr Arg Ile Ser Glu Leu Lys Ala	
50 55 60	
GAA GCA GTG AAG AAG GAC CGC AGA AAG AAG CTG ACC CAG TCC AAG TTT	238
Glu Ala Val Lys Lys Asp Arg Arg Lys Lys Leu Thr Gln Ser Lys Phe	
65 70 75	
GTC GGG GGA GCC GAG AAC ACT GCC CAC CCC CGG ATC ATC TCT GAA CCT	286
Val Gly Gly Ala Glu Asn Thr Ala His Pro Arg Ile Ile Ser Glu Pro	
80 85 90 95	
GAG ATG AGA CAG GAG TCT GAG CAG GGC CCC TGC CGC AGA CAC ATG GAG	334
Glu Met Arg Gln Glu Ser Glu Gln Gly Pro Cys Arg Arg His Met Glu	
100 105 110	
GCT TCC CTG CAG GAG CTC AAA GCC AGC CCA CGC ATG GTG CCC CGT GCT	382
Ala Ser Leu Gln Glu Leu Lys Ala Ser Pro Arg Met Val Pro Arg Ala	
115 120 125	
GTG TAC CTG CCC AAT TGT GAC CGC AAA GGA TTC TAC AAG AGA AAG CAG	430
Val Tyr Leu Pro Asn Cys Asp Arg Lys Gly Phe Tyr Lys Arg Lys Gln	
130 135 140	
TGC AAA CCT TCC CGT GGC CGC AAG CGT GGC ATC TGC TGG TGC GTG GAC	478
Cys Lys Pro Ser Arg Gly Arg Lys Arg Gly Ile Cys Trp Cys Val Asp	
145 150 155	
AAG TAC GGG ATG AAG CTG CCA GGC ATG GAG TAC GTT GAC GGG GAC TTT	526
Lys Tyr Gly Met Lys Leu Pro Gly Met Glu Tyr Val Asp Gly Asp Phe	
160 165 170 175	
CAG TGC CAC ACC TTC GAC AGC AGC AAC GTT GAG TGATGCGTCC CCCCCCAACC	579
Gln Cys His Thr Phe Asp Ser Ser Asn Val Glu	
180 185	
TTTCCCTCAC CCCCTTCCAC CCCAGCCCC GACTCCAGCC AGCGCCTCCC TCCACCCCAG	639

GACGCCACTC ATTTCATCTC ATTTAAGGGA AAAATATATA TCTATCTATT TGAGGAAAAA 699  
 AAAAAAAAAA AAAAAAAAAA AAA 722

## (2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 186 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Glu Lys Pro Leu His Ala Leu Leu His Gly Arg Gly Val Cys Leu Asn  
 1 5 10 15  
 Glu Lys Ser Tyr Arg Glu Gln Val Lys Ile Glu Arg Asp Ser Arg Glu  
 20 25 30  
 His Glu Glu Pro Thr Thr Ser Glu Met Ala Glu Glu Thr Tyr Ser Pro  
 35 40 45  
 Lys Ile Phe Arg Pro Lys His Thr Arg Ile Ser Glu Leu Lys Ala Glu  
 50 55 60  
 Ala Val Lys Lys Asp Arg Arg Lys Lys Leu Thr Gln Ser Lys Phe Val  
 65 70 75 80  
 Gly Gly Ala Glu Asn Thr Ala His Pro Arg Ile Ile Ser Glu Pro Glu  
 85 90 95  
 Met Arg Gln Glu Ser Glu Gln Gly Pro Cys Arg Arg His Met Glu Ala  
 100 105 110  
 Ser Leu Gln Glu Leu Lys Ala Ser Pro Arg Met Val Pro Arg Ala Val  
 115 120 125  
 Tyr Leu Pro Asn Cys Asp Arg Lys Gly Phe Tyr Lys Arg Lys Gln Cys  
 130 135 140  
 Lys Pro Ser Arg Gly Arg Lys Arg Gly Ile Cys Trp Cys Val Asp Lys  
 145 150 155 160  
 Tyr Gly Met Lys Leu Pro Gly Met Glu Tyr Val Asp Gly Asp Phe Gln  
 165 170 175  
 Cys His Thr Phe Asp Ser Ser Asn Val Glu  
 180 185

## (2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1023 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

- (ix) FEATURE:  
 (A) NAME/KEY: CDS

(B) LOCATION: 57..875

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCCTGCACTC TCGCTCTCCT GCCCCACCCC GAGGTAAAGG GGGCGACTAA GAGAAG	56
ATG GTG TTG CTC ACC GCG GTC CTC CTG CTG CTG GCC GCC TAT GCG GGG Met Val Leu Leu Thr Ala Val Leu Leu Leu Ala Ala Tyr Ala Gly	104
CCG GCC CAG AGC CTG GGC TCC TTC GTG CAC TGC GAG CCC TGC GAC GAG Pro Ala Gln Ser Leu Gly Ser Phe Val His Cys Glu Pro Cys Asp Glu	152
AAA GCC CTC TCC ATG TGC CCC CCC AGC CCC CTG GGC TGC GAG CTG GTC Lys Ala Leu Ser Met Cys Pro Pro Ser Pro Leu Gly Cys Glu Leu Val	200
AAG GAG CCG GGC TGC GGC TGC TGC ATG ACC TGC GCC CTG GCC GAG GGG Lys Glu Pro Gly Cys Gly Cys Cys Met Thr Cys Ala Leu Ala Glu Gly	248
CAG TCG TGC GGC GTC TAC ACC GAG CGC TGC GCC CAG GGG CTG CGC TGC Gln Ser Cys Gly Val Tyr Thr Glu Arg Cys Ala Gln Gly Leu Arg Cys	296
CTC CCC CGG CAG GAC GAG GAG AAG CCG CTG CAC GCC CTG CTG CAC GGC Leu Pro Arg Gln Asp Glu Glu Lys Pro Leu His Ala Leu Leu His Gly	344
CGC GGG GTT TGC CTC AAC GAA AAG AGC TAC CGC GAG CAA GTC AAG ATC Arg Gly Val Cys Leu Asn Glu Lys Ser Tyr Arg Glu Gln Val Lys Ile	392
GAG AGA GAC TCC CGT GAG CAC GAG GAG CCC ACC ACC TCT GAG ATG GCC Glu Arg Asp Ser Arg Glu His Glu Glu Pro Thr Thr Ser Glu Met Ala	440
GAG GAG ACC TAC TCC CCC AAG ATC TTC CGG CCC AAA CAC ACC CGC ATC Glu Glu Thr Tyr Ser Pro Lys Ile Phe Arg Pro Lys His Thr Arg Ile	488
TCC GAG CTG AAG GCT GAA GCA GTG AAG AAG GAC CGC AGA AAG AAG CTG Ser Glu Leu Lys Ala Glu Ala Val Lys Lys Asp Arg Arg Lys Lys Leu	536
ACC CAG TCC AAG TTT GTC GGG GGA GCC GAG AAC ACT GCC CAC CCC CGG Thr Gln Ser Lys Phe Val Gly Gly Ala Glu Asn Thr Ala His Pro Arg	584
ATC ATC TCT GCA CCT GAG ATG AGA CAG GAG TCT GAG CAG GGC CCC TGC Ile Ile Ser Ala Pro Glu Met Arg Gln Glu Ser Glu Gln Gly Pro Cys	632
CGC AGA CAC ATG GAG GCT TCC CTG CAG GAG CTC AAA GCC AGC CCA CGC Arg Arg His Met Glu Ala Ser Leu Gln Glu Leu Lys Ala Ser Pro Arg	680
ATG GTG CCC CGT GCT GTG TAC CTG CCC AAT TGT GAC CGC AAA GGA TTC Met Val Pro Arg Ala Val Tyr Leu Pro Asn Cys Asp Arg Lys Gly Phe	728
TAC AAG AGA AAG CAG TGC AAA CCT TCC CGT GGC CGC AAG CGT GGC ATC Tyr Lys Arg Lys Gln Cys Lys Pro Ser Arg Gly Arg Lys Arg Gly Ile	776

```

TGC TGG TGC GTG GAC AAG TAC GGG ATG AAG CTG CCA GGC ATG GAG TAC      824
Cys Trp Cys Val Asp Lys Tyr Gly Met Lys Leu Pro Gly Met Glu Tyr
      245                      250                      255

GTT GAC GGG GAC TTT CAG TGC CAC ACC TTC GAC AGC AGC AAC GTT GAG      872
Val Asp Gly Asp Phe Gln Cys His Thr Phe Asp Ser Ser Asn Val Glu
      260                      265                      270

TGATGCGTCC CCCCCCAACC TTTCCTCTCAG CCCCCTCCAC CCCCAGCCCC GACTCCAGCC      932
AGCGCCTCCC TCCACCCGAG GACGCCACTC ATTTCTCTCT ATTTAAGGGA AAAATATATA      992
TCTATCTATT TGAAAAAAAA AAAAAAACC C                                1023

```

## (2) INFORMATION FOR SEQ ID NO:8:

## (1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (11) MOLECULE TYPE: protein

## (x1) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```

Met Val Leu Leu Thr Ala Val Leu Leu Leu Leu Ala Ala Tyr Ala Gly
  1                      5                      10                      15

Pro Ala Gln Ser Leu Gly Ser Phe Val His Cys Glu Pro Cys Asp Glu
      20                      25                      30

Lys Ala Leu Ser Met Cys Pro Pro Ser Pro Leu Gly Cys Glu Leu Val
      35                      40                      45

Lys Glu Pro Gly Cys Gly Cys Cys Met Thr Cys Ala Leu Ala Glu Gly
      50                      55                      60

Gln Ser Cys Gly Val Tyr Thr Glu Arg Cys Ala Gln Gly Leu Arg Cys
      65                      70                      75                      80

Leu Pro Arg Gln Asp Glu Glu Lys Pro Leu His Ala Leu Leu His Gly
      85                      90                      95

Arg Gly Val Cys Leu Asn Glu Lys Ser Tyr Arg Glu Gln Val Lys Ile
      100                      105                      110

Glu Arg Asp Ser Arg Glu His Glu Glu Pro Thr Thr Ser Glu Met Ala
      115                      120                      125

Glu Glu Thr Tyr Ser Pro Lys Ile Phe Arg Pro Lys His Thr Arg Ile
      130                      135                      140

Ser Glu Leu Lys Ala Glu Ala Val Lys Lys Asp Arg Arg Lys Lys Leu
      145                      150                      155                      160

Thr Gln Ser Lys Phe Val Gly Gly Ala Glu Asn Thr Ala His Pro Arg
      165                      170                      175

Ile Ile Ser Ala Pro Glu Met Arg Gln Glu Ser Glu Gln Gly Pro Cys
      180                      185                      190

Arg Arg His Met Glu Ala Ser Leu Gln Glu Leu Lys Ala Ser Pro Arg
      195                      200                      205

Met Val Pro Arg Ala Val Tyr Leu Pro Asn Cys Asp Arg Lys Gly Phe
      210                      215                      220

```

Tyr Lys Arg Lys Gln Cys Lys Pro Ser Arg Gly Arg Lys Arg Gly Ile  
 225 230 235 240  
 Cys Trp Cys Val Asp Lys Tyr Gly Met Lys Leu Pro Gly Met Glu Tyr  
 245 250 255  
 Val Asp Gly Asp Phe Gln Cys His Thr Phe Asp Ser Ser Asn Val Glu  
 260 265 270

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1694 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (iii) HYPOTHETICAL: NO

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 2..931

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

C TCT CTC AAG GCC AAC ATC CCT GAG GTG GAA GCT GTC CTC AAC ACC	46
Ser Leu Lys Ala Asn Ile Pro Glu Val Glu Ala Val Leu Asn Thr	
1 5 10 15	
GAC AGG AGT TTG GTG TGT GAT GGG AAG AGG GGC TTA TTA ACT CGT CTG	94
Asp Arg Ser Leu Val Cys Asp Gly Lys Arg Gly Leu Leu Thr Arg Leu	
20 25 30	
CTG CAG GTC ATG AAG AAG GAG CCA GCA GAG TCG TCT TTC AGG TTT TGG	142
Leu Gln Val Met Lys Lys Glu Pro Ala Glu Ser Ser Phe Arg Phe Trp	
35 40 45	
CAA GCT CGG GCT GTG GAG AGT TTC CTC CGA GGG ACC ACC TCC TAT GCA	190
Gln Ala Arg Ala Val Glu Ser Phe Leu Arg Gly Thr Thr Ser Tyr Ala	
50 55 60	
GAC CAG ATG TTC CTG CTG AAG CGA GGC CTC TTG GAG CAC ATC CTT TAC	238
Asp Gln Met Phe Leu Leu Lys Arg Gly Leu Leu Glu His Ile Leu Tyr	
65 70 75	
TGC ATT GTG GAC AGC GAG TGT AAG TCA AGG GAT GTG CTC CAG AGT TAC	286
Cys Ile Val Asp Ser Glu Cys Lys Ser Arg Asp Val Leu Gln Ser Tyr	
80 85 90 95	
TTT GAC CTC CTG GGG GAG CTG ATG AAG TTC AAC GTT GAT GCA TTC AAG	334
Phe Asp Leu Leu Gly Glu Leu Met Lys Phe Asn Val Asp Ala Phe Lys	
100 105 110	
AGA TTC AAT AAA TAT ATC AAC ACC GAT GCA AAG TTC CAG GTA TTC CTG	382
Arg Phe Asn Lys Tyr Ile Asn Thr Asp Ala Lys Phe Gln Val Phe Leu	
115 120 125	



AAG CAG ATC AAC AGC TCC CTG GTG GAC TCC AAC ATG CTG GTG CGC TGT	430
Lys Gln Ile Asn Ser Ser Leu Val Asp Ser Asn Met Leu Val Arg Cys	
130 135 140	
GTC ACT CTG TCC CTG GAC CGA TTT GAA AAC CAG GTG GAT ATG AAA GTT	478
Val Thr Leu Ser Leu Asp Arg Phe Glu Asn Gln Val Asp Met Lys Val	
145 150 155	
GCC GAG GTA CTG TCT GAA TGC CGC CTG CTC GCC TAC ATA TCC CAG GTG	526
Ala Glu Val Leu Ser Glu Cys Arg Leu Leu Ala Tyr Ile Ser Gln Val	
160 165 170 175	
CCC ACG CAG ATG TCC TTC CTC TTC CGC CTC ATC AAC ATC ATC CAC GTG	574
Pro Thr Gln Met Ser Phe Leu Phe Arg Leu Ile Asn Ile Ile His Val	
180 185 190	
CAG ACG CTG ACC CAG GAG AAC GTC AGC TGC CTC AAC ACC AGC CTG GTG	622
Gln Thr Leu Thr Gln Glu Asn Val Ser Cys Leu Asn Thr Ser Leu Val	
195 200 205	
ATC CTG ATG CTG GCC CGA CGG AAA GAG CGG CTG CCC CTG TAC CTG CGG	670
Ile Leu Met Leu Ala Arg Arg Lys Glu Arg Leu Pro Leu Tyr Leu Arg	
210 215 220	
CTG CTG CAG CGG ATG GAG CAC AGC AAG AAG TAC CCC GGC TTC CTG CTC	718
Leu Leu Gln Arg Met Glu His Ser Lys Lys Tyr Pro Gly Phe Leu Leu	
225 230 235	
AAC AAC TTC CAC AAC CTG CTG CGC TTC TGG CAG CAG CAC TAC CTG CAC	766
Asn Asn Phe His Asn Leu Leu Arg Phe Trp Gln Gln His Tyr Leu His	
240 245 250 255	
AAG GAC AAG GAC AGC ACC TGC CTA GAG AAC AGC TCC TGC ATC AGC TTC	814
Lys Asp Lys Asp Ser Thr Cys Leu Glu Asn Ser Ser Cys Ile Ser Phe	
260 265 270	
TCA TAC TGG AAG GAG ACA GTG TCC ATC CTG TTG AAC CCG GAC CGG CAG	862
Ser Tyr Trp Lys Glu Thr Val Ser Ile Leu Leu Asn Pro Asp Arg Gln	
275 280 285	
TCA CCC TCT GCT CTC GTT AGC TAC ATT GAG GAG CCC TAC ATG GAC ATA	910
Ser Pro Ser Ala Leu Val Ser Tyr Ile Glu Glu Pro Tyr Met Asp Ile	
290 295 300	
GAC AGG GAC TTC ACT GAG GAG TGACCTTGGG CCAGGCCTCG GGAGGCTGCT	961
Asp Arg Asp Phe Thr Glu Glu	
305 310	
GGGCCAGTGT GGGTGAGCGT GGGTACGATG CCACACGCCC TGCCCTGTTC CCGTTCCTCC	1021
CTGCTGCTCT CTGCCTGCCC CAGGTCTTTG GGTACAGGCT TGGTGGGAGG GAAGTCCTAG	1081
AAGCCCTTGG TCCCCCTGGG TCTGAGGGCC CTAGGTCATG GAGAGCCTCA GTCCCCATAA	1141
TGAGGACAGG GTACCATGCC CACCTTTCCT TCAGAACCCT GGGGCCCAGG GCCACCCAGA	1201
GGTAAGAGGA CATTTAGCAT TAGCTCTGTG TGAGCTCCTG CCGGTTTCTT GGCTGTCACT	1261
CAGTCCCAGA GTGGGGAGGA AGATATGGGT GACCCCCACC CCCCATCTGT GAGCCAAGCC	1321
TCCCTTGTC CTGGCCTTTG GACCCAGGCA AAGGCTTCTG AGCCCTGGGC AGGGGTGGTG	1381
GGTACCAGAG AATGCTGCCT TCCCCAAGC CTGCCCTCT GCCTCATTTT CCTGTAGCTC	1441
CTCTGGTTCT GTTTGCTCAT TGGCCGCTGT GTTCATCCAA GGGGGTTCTC CCAGAAGTGA	1501
GGGGCCTTTC CCTCCATCCC TTGGGGCAGC GGGCAGCTGT GCCTGCCCTG CCTCTGCCTG	1561

AGGCAGCCGC TCCTGCCTGA GCCTGGACAT GGGGCCCTTC CTTGTGTTGC CAATTTATTA 1621  
 ACAGCAAATA AACCAATTAA ATGGAGACTA TTAAATAACT TTATTTTAAA AATGAAAAAA 1681  
 AAAAAAAAAA AAA 1694

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 310 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Ser Leu Lys Ala Asn Ile Pro Glu Val Glu Ala Val Leu Asn Thr Asp  
 1 5 10 15  
 Arg Ser Leu Val Cys Asp Gly Lys Arg Gly Leu Leu Thr Arg Leu Leu  
 20 25 30  
 Gln Val Met Lys Lys Glu Pro Ala Glu Ser Ser Phe Arg Phe Trp Gln  
 35 40 45  
 Ala Arg Ala Val Glu Ser Phe Leu Arg Gly Thr Thr Ser Tyr Ala Asp  
 50 55 60  
 Gln Met Phe Leu Leu Lys Arg Gly Leu Leu Glu His Ile Leu Tyr Cys  
 65 70 75 80  
 Ile Val Asp Ser Glu Cys Lys Ser Arg Asp Val Leu Gln Ser Tyr Phe  
 85 90 95  
 Asp Leu Leu Gly Glu Leu Met Lys Phe Asn Val Asp Ala Phe Lys Arg  
 100 105 110  
 Phe Asn Lys Tyr Ile Asn Thr Asp Ala Lys Phe Gln Val Phe Leu Lys  
 115 120 125  
 Gln Ile Asn Ser Ser Leu Val Asp Ser Asn Met Leu Val Arg Cys Val  
 130 135 140  
 Thr Leu Ser Leu Asp Arg Phe Glu Asn Gln Val Asp Met Lys Val Ala  
 145 150 155 160  
 Glu Val Leu Ser Glu Cys Arg Leu Leu Ala Tyr Ile Ser Gln Val Pro  
 165 170 175  
 Thr Gln Met Ser Phe Leu Phe Arg Leu Ile Asn Ile Ile His Val Gln  
 180 185 190  
 Thr Leu Thr Gln Glu Asn Val Ser Cys Leu Asn Thr Ser Leu Val Ile  
 195 200 205  
 Leu Met Leu Ala Arg Arg Lys Glu Arg Leu Pro Leu Tyr Leu Arg Leu  
 210 215 220  
 Leu Gln Arg Met Glu His Ser Lys Lys Tyr Pro Gly Phe Leu Leu Asn  
 225 230 235 240  
 Asn Phe His Asn Leu Leu Arg Phe Trp Gln Gln His Tyr Leu His Lys  
 245 250 255  
 Asp Lys Asp Ser Thr Cys Leu Glu Asn Ser Ser Cys Ile Ser Phe Ser

260 265 270  
 Tyr Trp Lys Glu Thr Val Ser Ile Leu Leu Asn Pro Asp Arg Gln Ser  
 275 280 285  
 Pro Ser Ala Leu Val Ser Tyr Ile Glu Glu Pro Tyr Met Asp Ile Asp  
 290 295 300  
 Arg Asp Phe Thr Glu Glu  
 305 310

## (ii) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2735 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (iii) HYPOTHETICAL: NO

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 2..1822

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

G GAG ATC AGT CGG AAG GTG TAC AAG GGA ATG TTA GAC CTC CTC AAG	46
Glu Ile Ser Arg Lys Val Tyr Lys Gly Met Leu Asp Leu Leu Lys	
1 5 10 15	
TGT ACA GTC CTC AGC TTG GAG CAG TCC TAT GCC CAC GCG GGT CTG GGT	94
Cys Thr Val Leu Ser Leu Glu Gln Ser Tyr Ala His Ala Gly Leu Gly	
20 25 30	
GGC ATG GCC AGC ATC TTT GGG CTT TTG GAG ATT GCC CAG ACC CAC TAC	142
Gly Met Ala Ser Ile Phe Gly Leu Leu Glu Ile Ala Gln Thr His Tyr	
35 40 45	
TAT AGT AAA GAA CCA GAC AAG CGG AAG AGA AGT CCA ACA GAA AGT GTA	190
Tyr Ser Lys Glu Pro Asp Lys Arg Lys Arg Ser Pro Thr Glu Ser Val	
50 55 60	
AAT ACC CCA GTT GGC AAG GAT CCT GGC CTA GCT GGG CGG GGG GAC CCA	238
Asn Thr Pro Val Gly Lys Asp Pro Gly Leu Ala Gly Arg Gly Asp Pro	
65 70 75	
AAG GCT ATG GCA CAA CTG AGA GTT CCA CAA CTG GGA CCT CGG GCA CCA	286
Lys Ala Met Ala Gln Leu Arg Val Pro Gln Leu Gly Pro Arg Ala Pro	
80 85 90 95	
AGT GCC ACA GGA AAG GGT CCT AAG GAA CTG GAC ACC AGA AGT TTA AAG	334
Ser Ala Thr Gly Lys Gly Pro Lys Glu Leu Asp Thr Arg Ser Leu Lys	
100 105 110	
GAA GAA AAT TTT ATA GCA TCT ATT GGG CCT GAA GTA ATC AAA CCT GTC	382
Glu Glu Asn Phe Ile Ala Ser Ile Gly Pro Glu Val Ile Lys Pro Val	
115 120 125	
TTT GAC CTT GGT GAG ACA GAG GAG AAA AAG TCC CAG ATC AGC GCA GAC	430
Phe Asp Leu Gly Glu Thr Glu Glu Lys Lys Ser Gln Ile Ser Ala Asp	
130 135 140	

AGT GGT GTG AGC CTG ACG TCT AGT TCC CAG AGG ACT GAT CAA GAC TCT Ser Gly Val Ser Leu Thr Ser Ser Ser Gln Arg Thr Asp Gln Asp Ser 145 150 155	478
GTC ATC GGC GTG AGT CCA GCT GTT ATG ATC CGC AGC TCA AGT CAG GAT Val Ile Gly Val Ser Pro Ala Val Met Ile Arg Ser Ser Ser Gln Asp 160 165 170 175	526
TCT GAA GTT AGC ACC GTG GTG AGT AAT AGC TCT GGA GAG ACC CTT GGA Ser Glu Val Ser Thr Val Val Ser Asn Ser Ser Gly Glu Thr Leu Gly 180 185 190	574
GCT GAC AGT GAC TTG AGC AGC AAT GCA GGT GAT GGA CCA GGT GGC GAG Ala Asp Ser Asp Leu Ser Ser Asn Ala Gly Asp Gly Pro Gly Gly Glu 195 200 205	622
GGC AGT GTT CAC CTG GCA AGC TCT CGG GGC ACT TTG TCT GAT AGT GAA Gly Ser Val His Leu Ala Ser Ser Arg Gly Thr Leu Ser Asp Ser Glu 210 215 220	670
ATT GAG ACC AAC TCT GCC ACA AGC ACC ATC TTT GGT AAA GCC CAC AGC Ile Glu Thr Asn Ser Ala Thr Ser Thr Ile Phe Gly Lys Ala His Ser 225 230 235	718
TTG AAG CCA AGC ATA AAG GAG AAG CTG GCA GGC AGC CCC ATT CGT ACT Leu Lys Pro Ser Ile Lys Glu Lys Leu Ala Gly Ser Pro Ile Arg Thr 240 245 250 255	766
TCT GAA GAT GTG AGC CAG CGA GTC TAT CTC TAT GAG GGA CTC CTA GGC Ser Glu Asp Val Ser Gln Arg Val Tyr Leu Tyr Glu Gly Leu Leu Gly 260 265 270	814
AAA GAG CGT TCT ACT TTA TGG GAC CAA ATG CAA TTC TGG GAA GAT GCC Lys Glu Arg Ser Thr Leu Trp Asp Gln Met Gln Phe Trp Glu Asp Ala 275 280 285	862
TTC TTA GAT GCT GTG ATG TTG GAG AGA GAA GGG ATG GGT ATG GAC CAG Phe Leu Asp Ala Val Met Leu Glu Arg Glu Gly Met Gly Met Asp Gln 290 295 300	910
GGT CCC CAG GAA ATG ATC GAC AGG TAC CTG TCC CTT GGA GAA CAT GAC Gly Pro Gln Glu Met Ile Asp Arg Tyr Leu Ser Leu Gly Glu His Asp 305 310 315	958
CGG AAG CGC CTG GAA GAT GAT GAA GAT CGC TTG CTG GCC ACA CTT CTG Arg Lys Arg Leu Glu Asp Asp Glu Asp Arg Leu Leu Ala Thr Leu Leu 320 325 330 335	1006
CAC AAC CTC ATC TCC TAC ATG CTG CTG ATG AAG GTA AAT AAG AAT GAC His Asn Leu Ile Ser Tyr Met Leu Leu Met Lys Val Asn Lys Asn Asp 340 345 350	1054
ATC CGC AAG AAG GTG AGG CGC CTA ATG GGA AAG TCG CAC ATT GGG CTT Ile Arg Lys Lys Val Arg Arg Leu Met Gly Lys Ser His Ile Gly Leu 355 360 365	1102
GTG TAC AGC CAG CAA ATC AAT GAG GTG CTT GAT CAG CTG GCG AAC CTG Val Tyr Ser Gln Gln Ile Asn Glu Val Leu Asp Gln Leu Ala Asn Leu 370 375 380	1150
AAT GGA CGC GAT CTC TCT ATC TGG TCC AGT GGC AGC CGG CAC ATG AAG Asn Gly Arg Asp Leu Ser Ile Trp Ser Ser Gly Ser Arg His Met Lys 385 390 395	1198
AAG CAG ACA TTT GTG GTA CAT GCA GGG ACA GAT ACA AAC GGA GAT ATC Lys Gln Thr Phe Val Val His Ala Gly Thr Asp Thr Asn Gly Asp Ile 400 405 410 415	1246

TTT TTC ATG GAG GTG TGC GAT GAC TGT GTG GTG TTG CGT AGT AAC ATC	1294
Phe Phe Met Glu Val Cys Asp Asp Cys Val Val Leu Arg Ser Asn Ile	
420 425 430	
GGG ACA GTG TAT GAG CGC TGG TGG TAC GAG AAG CTC ATC AAC ATG ACC	1342
Gly Thr Val Tyr Glu Arg Trp Trp Tyr Glu Lys Leu Ile Asn Met Thr	
435 440 445	
TAC TGT CCC AAG ACG AAG GTG TTG TGC TTG TGG CGT AGA AAT GGC TCT	1390
Tyr Cys Pro Lys Thr Lys Val Leu Cys Leu Trp Arg Asn Gly Ser	
450 455 460	
GAG ACC CAG CTC AAC AAG TTC TAT ACT AAA AAG TGT CGG GAG CTG TAC	1438
Glu Thr Gln Leu Asn Lys Phe Tyr Thr Lys Lys Cys Arg Glu Leu Tyr	
465 470 475	
TAC TGT GTG AAG GAC AGC ATG GAG CGC GCT GCC GCC CGA CAG CAA AGC	1486
Tyr Cys Val Lys Asp Ser Met Glu Arg Ala Ala Ala Arg Gln Gln Ser	
480 485 490 495	
ATC AAA CCC GGA CCT GAA TTG GGT GGC GAG TTC CCT GTG CAG GAC CTG	1534
Ile Lys Pro Gly Pro Glu Leu Gly Gly Glu Phe Pro Val Gln Asp Leu	
500 505 510	
AAG ACT GST GAG GGT GGC CTG CTG CAG GTG ACC CTG GAA GGG ATC AAC	1582
Lys Thr Gly Glu Gly Gly Leu Leu Gln Val Thr Leu Glu Gly Ile Asn	
515 520 525	
CTC AAA TTC ATG CAC AAT CAG GTT TTC ATA GAG CTG AAT CAC ATT AAA	1630
Leu Lys Phe Met His Asn Gln Val Phe Ile Glu Leu Asn His Ile Lys	
530 535 540	
AAG TGC AAT ACA GTT CGA GGC GTC TTT GTC CTG GAG GAA TTT GTT CCT	1678
Lys Cys Asn Thr Val Arg Gly Val Phe Val Leu Glu Glu Phe Val Pro	
545 550 555	
GAA ATT AAA GAA GTG GTG AGC CAC AAG TAC AAG ACA CCA ATG GCC CAC	1726
Glu Ile Lys Glu Val Val Ser His Lys Tyr Lys Thr Pro Met Ala His	
560 565 570 575	
GAA ATC TGC TAC TCC GTA TTA TGT CTC TTC TCG TAC GTG GCT GCA GTT	1774
Glu Ile Cys Tyr Ser Val Leu Cys Leu Phe Ser Tyr Val Ala Ala Val	
580 585 590	
CAT AGC AGT GAG GAA GAT CTC AGA ACC CCG CCC CGG CCT GTC TCT AGC	1822
His Ser Ser Glu Glu Asp Leu Arg Thr Pro Pro Arg Pro Val Ser Ser	
595 600 605	
TGATGGAGAG GGGCTACGCA GCTGCCCCAG CCCAGGGCAC GCCCCTGGCC CCTTGCTGTT	1882
CCCCAAGTGCA CGATGCTGCT GTGACTGAGG AGTGGATGAT GCTCGTGTGT CCTCTGCAAG	1942
CCCCCTGCTG TGGCTTGGTT GGTTACCGGT TATGTGTCCC TCTGAGTGTG TCTTGAGCGT	2002
GTCCACCTTC TCCCTCTCCA CTCCCAGAAG ACCAACTGC CTCCCCCTCA GGGCTCAAGA	2062
ATGTGTACAG TCTGTGGGGC CGGTGTGAAC CCACTATTTT GTGTCCTTGA GACATTTGTG	2122
TTGTGGTTCC TTGTCCTTGT CCCTGGCGTT ATAAGTGTCC ACTGCAAGAG TCTGGCTCTC	2182
CCTTCTCTGT GACCCGGCAT GACTGGGCGC CTGGAGCAGT TTCACTCTGT GAGGAGTGAG	2242
GGAACCCCTGG GGCTCACCTC CTCAGAGGAA GGGCACAGAG AGGAAGGGAA GAATTGGGGG	2302
GCAGCCGGAG TGAGTGGCAG CCTCCCTGCT TCCTTCTGCA TTCCCAAGCC GGCAGCTACT	2362
GCCCAGGGCC CGCAGTGTTG GCTGCTGCCT GCCACAGCCT CTGTGACTGC AGTGGAGCGG	2422

CGAATTCCCT GTGGCCTGCC ACGCCTTCGG CATCAGAGGA TGGAGTGGTC GAGGCTAGTG	2482
GAGTCCCAGG GACCGCTGGC TGCTCTGCCT GAGCATCAGG GAGGGGGCAG GAAAGACCAA	2542
GCTGGGTTTG CACATCTGTC TGCAGGCTGT CTCTCCAGGC ACGGGGTGTC AGGAGGGAGA	2602
GACAGCCTGG GTATGGGCAA GAAATGACTG TAAATATTTT AGCCCCACAT TATTTATAGA	2662
AAATGTACAG TTGTGTGAAT GTGAAATAAA TGTCCTCAAC TCCCAAAAAA AAAAAAAAAA	2722
AAAAAAAAAA AAA	2735

## (2) INFORMATION FOR SEQ ID NO:12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 607 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Glu	Ile	Ser	Arg	Lys	Val	Tyr	Lys	Gly	Met	Leu	Asp	Leu	Leu	Lys	Cys	1	5	10	15
Thr	Val	Leu	Ser	Leu	Glu	Gln	Ser	Tyr	Ala	His	Ala	Gly	Leu	Gly	Gly	20	25	30	
Met	Ala	Ser	Ile	Phe	Gly	Leu	Leu	Glu	Ile	Ala	Gln	Thr	His	Tyr	Tyr	35	40	45	
Ser	Lys	Glu	Pro	Asp	Lys	Arg	Lys	Arg	Ser	Pro	Thr	Glu	Ser	Val	Asn	50	55	60	
Thr	Pro	Val	Gly	Lys	Asp	Pro	Gly	Leu	Ala	Gly	Arg	Gly	Asp	Pro	Lys	65	70	75	80
Ala	Met	Ala	Gln	Leu	Arg	Val	Pro	Gln	Leu	Gly	Pro	Arg	Ala	Pro	Ser	85	90	95	
Ala	Thr	Gly	Lys	Gly	Pro	Lys	Glu	Leu	Asp	Thr	Arg	Ser	Leu	Lys	Glu	100	105	110	
Glu	Asn	Phe	Ile	Ala	Ser	Ile	Gly	Pro	Glu	Val	Ile	Lys	Pro	Val	Phe	115	120	125	
Asp	Leu	Gly	Glu	Thr	Glu	Glu	Lys	Lys	Ser	Gln	Ile	Ser	Ala	Asp	Ser	130	135	140	
Gly	Val	Ser	Leu	Thr	Ser	Ser	Ser	Gln	Arg	Thr	Asp	Gln	Asp	Ser	Val	145	150	155	160
Ile	Gly	Val	Ser	Pro	Ala	Val	Met	Ile	Arg	Ser	Ser	Ser	Gln	Asp	Ser	165	170	175	
Glu	Val	Ser	Thr	Val	Val	Ser	Asn	Ser	Ser	Gly	Glu	Thr	Leu	Gly	Ala	180	185	190	
Asp	Ser	Asp	Leu	Ser	Ser	Asn	Ala	Gly	Asp	Gly	Pro	Gly	Gly	Glu	Gly	195	200	205	
Ser	Val	His	Leu	Ala	Ser	Ser	Arg	Gly	Thr	Leu	Ser	Asp	Ser	Glu	Ile	210	215	220	
Glu	Thr	Asn	Ser	Ala	Thr	Ser	Thr	Ile	Phe	Gly	Lys	Ala	His	Ser	Leu				

225		230		235		240
Lys Pro Ser Ile	Lys Glu Lys Leu Ala	Gly Ser Pro Ile Arg Thr Ser				
	245	250			255	
Glu Asp Val Ser	Gln Arg Val Tyr Leu Tyr Glu Gly Leu Leu Gly Lys					
	260	265			270	
Glu Arg Ser Thr	Leu Trp Asp Gln Met Gln Phe Trp Glu Asp Ala Phe					
	275	280			285	
Leu Asp Ala Val Met	Leu Glu Arg Glu Gly Met Gly Met Asp Gln Gly					
	290	295		300		
Pro Gln Glu Met Ile	Asp Arg Tyr Leu Ser Leu Gly Glu His Asp Arg					
305	310	315			320	
Lys Arg Leu Glu Asp	Asp Glu Asp Arg Leu Leu Ala Thr Leu Leu His					
	325	330			335	
Asn Leu Ile Ser	Tyr Met Leu Leu Met Lys Val Asn Lys Asn Asp Ile					
	340	345			350	
Arg Lys Lys Val Arg	Arg Leu Met Gly Lys Ser His Ile Gly Leu Val					
	355	360			365	
Tyr Ser Gln Gln Ile	Asn Glu Val Leu Asp Gln Leu Ala Asn Leu Asn					
	370	375		380		
Gly Arg Asp Leu Ser	Ile Trp Ser Ser Gly Ser Arg His Met Lys Lys					
385	390	395			400	
Gln Thr Phe Val Val	His Ala Gly Thr Asp Thr Asn Gly Asp Ile Phe					
	405	410			415	
Phe Met Glu Val Cys	Asp Asp Cys Val Val Leu Arg Ser Asn Ile Gly					
	420	425			430	
Thr Val Tyr Glu Arg	Trp Trp Tyr Glu Lys Leu Ile Asn Met Thr Tyr					
	435	440			445	
Cys Pro Lys Thr Lys	Val Leu Cys Leu Trp Arg Arg Asn Gly Ser Glu					
	450	455		460		
Thr Gln Leu Asn Lys	Phe Tyr Thr Lys Lys Cys Arg Glu Leu Tyr Tyr					
465	470	475			480	
Cys Val Lys Asp Ser	Met Glu Arg Ala Ala Ala Arg Gln Gln Ser Ile					
	485	490			495	
Lys Pro Gly Pro	Glu Leu Gly Gly Glu Phe Pro Val Gln Asp Leu Lys					
	500	505			510	
Thr Gly Glu Gly	Gly Leu Leu Gln Val Thr Leu Glu Gly Ile Asn Leu					
	515	520			525	
Lys Phe Met His	Asn Gln Val Phe Ile Glu Leu Asn His Ile Lys Lys					
	530	535		540		
Cys Asn Thr Val Arg	Gly Val Phe Val Leu Glu Glu Phe Val Pro Glu					
545	550	555			560	
Ile Lys Glu Val Val	Ser His Lys Tyr Lys Thr Pro Met Ala His Glu					
	565	570			575	
Ile Cys Tyr Ser	Val Leu Cys Leu Phe Ser Tyr Val Ala Ala Val His					
	580	585			590	

Ser Ser Glu Glu Asp Leu Arg Thr Pro Pro Arg Pro Val Ser Ser  
 595 600 605

## (2) INFORMATION FOR SEQ ID NO:13:

- (1) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 3225 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

## (ix) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 3..2846

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CC CAG ACT CGC CCC GCC CCA GAG ACT GCG CCT GCG CGG GCA CGA GAC	47
Gln Thr Arg Pro Ala Pro Glu Thr Ala Pro Ala Arg Ala Arg Asp	
1 5 10 15	
ACC CTC TCC GCG ATG ACT GCC AGC TCA GTG GAG CAG CTG CGG AAG GAG	95
Thr Leu Ser Ala Met Thr Ala Ser Ser Val Glu Gln Leu Arg Lys Glu	
20 25 30	
GGC AAT GAG CTG TTC AAA TGT GGA GAC TAC GGG GGC GCC CTG GCG GCC	143
Gly Asn Glu Leu Phe Lys Cys Gly Asp Tyr Gly Gly Ala Leu Ala Ala	
35 40 45	
TAC ACT CAG GCC CTG GGT CTG GAC GCG ACG CCC CAG GAC CAG GCC GTT	191
Tyr Thr Gln Ala Leu Gly Leu Asp Ala Thr Pro Gln Asp Gln Ala Val	
50 55 60	
CTG CAC CGG AAC CGG GCC GCC TGC CAC CTC AAG CTG GAA GAT TAC GAC	239
Leu His Arg Asn Arg Ala Ala Cys His Leu Lys Leu Glu Asp Tyr Asp	
65 70 75	
AAA GCA GAA ACA GAG GCA TCC AAA GCC ATT GAA AAG GAT GGT GGG GAT	287
Lys Ala Glu Thr Glu Ala Ser Lys Ala Ile Glu Lys Asp Gly Gly Asp	
80 85 90 95	
GTC AAA GCA CTC TAC CGG CGG AGC CAA GCC CTA GAG AAG CTG GGC CGC	335
Val Lys Ala Leu Tyr Arg Arg Ser Gln Ala Leu Glu Lys Leu Gly Arg	
100 105 110	
CTG GAC CAG GCT GTC CTT GAC CTG CAG AGA TGT GTG AGC TTG GAG CCC	383
Leu Asp Gln Ala Val Leu Asp Leu Gln Arg Cys Val Ser Leu Glu Pro	
115 120 125	
AAG AAC AAA GTT TTC CAG GAG GCC TTG CGG AAC ATC GGG GGC CAG ATT	431
Lys Asn Lys Val Phe Gln Glu Ala Leu Arg Asn Ile Gly Gly Gln Ile	
130 135 140	
CAG GAG AAG GTG CGA TAC ATG TCC TCG ACG GAT GCC AAA GTG GAA CAG	479
Gln Glu Lys Val Arg Tyr Met Ser Ser Thr Asp Ala Lys Val Glu Gln	
145 150 155	



ATG TTT CAG ATA CTG TTG GAC CCA GAA GAG AAG GGC ACT GAG AAA AAG Met Phe Gln Ile Leu Leu Asp Pro Glu Glu Lys Gly Thr Glu Lys Lys 160 165 170 175	527
CAA AAG GGT TCT CAG AAC CTG GTG GTG CTG GCC AGG GAG GAT GGT GGA Gln Lys Ala Ser Gln Asn Leu Val Val Leu Ala Arg Glu Asp Ala Gly 180 185 190	575
GCG GAG AAG ATC TTC CGG AGT AAT GGG GTT CAG CTC TTG CAA CGT TTA Ala Glu Lys Ile Phe Arg Ser Asn Gly Val Gln Leu Leu Gln Arg Leu 195 200 205	623
CTG GAC ATG GGA GAG ACT GAC CTC ATG CTG GCG GCT CTG CGT ACG CTG Leu Asp Met Gly Glu Thr Asp Leu Met Leu Ala Ala Leu Arg Thr Leu 210 215 220	671
GTT GGC ATT TGC TCT GAG CAT CAG TCA CGG ACA GTG GCA ACC CTG AGC Val Gly Ile Cys Ser Glu His Gln Ser Arg Thr Val Ala Thr Leu Ser 225 230 235	719
ATA CTG GGA ACT CGG CGA GTA GTC TCC ATC CTG GGC GTG GAA AGC CAG Ile Leu Gly Thr Arg Arg Val Val Ser Ile Leu Gly Val Glu Ser Gln 240 245 250 255	767
GCT GTG TCC CTG GCT GCC TGC CAC CTG CTG CAG GTT ATG TTT GAT GCC Ala Val Ser Leu Ala Ala Cys His Leu Leu Gln Val Met Phe Asp Ala 260 265 270	815
CTC AAG GAA GGT GTC AAA AAA GGC TTC CGA GGC AAA GAA GGT GCC ATC Leu Lys Glu Gly Val Lys Lys Gly Phe Arg Gly Lys Glu Gly Ala Ile 275 280 285	863
ATT GTG GAT CCT GCC CGG GAG CTG AAG GTC CTC ATC AGT AAC CTC TTA Ile Val Asp Pro Ala Arg Glu Leu Lys Val Leu Ile Ser Asn Leu Leu 290 295 300	911
GAT CTG CTG ACA GAG GTG GGG GTC TCT GGC CAA GGC CGA GAC AAT GCC Asp Leu Leu Thr Glu Val Gly Val Ser Gly Gln Gly Arg Asp Asn Ala 305 310 315	959
CTG ACC CTC CTG ATT AAA GCG GTG CCC CGG AAG TCT CTC AAG GAC CCC Leu Thr Leu Leu Ile Lys Ala Val Pro Arg Lys Ser Leu Lys Asp Pro 320 325 330 335	1007
AAC AAC AGC CTC ACC CTC TGG GTC ATC GAC CAA GGT CTG AAA AAG ATT Asn Asn Ser Leu Thr Leu Trp Val Ile Asp Gln Gly Leu Lys Lys Ile 340 345 350	1055
TTG GAA GTG GGG GGC TCT CTA CAG GAC CCT CCT GGG GAG CTC GCA GTG Leu Glu Val Gly Ser Leu Gln Asp Pro Pro Gly Glu Leu Ala Val 355 360 365	1103
ACC GCA AAC AGC CGC ATG AGC GCC TCT ATT CTC CTC AGC AAG CTC TTT Thr Ala Asn Ser Arg Met Ser Ala Ser Ile Leu Leu Ser Lys Leu Phe 370 375 380	1151
GAT GAC CTC AAG TGT GAT GCG GAG AGG GAG AAT TTC CAC AGA CTT TGT Asp Asp Leu Lys Cys Asp Ala Glu Arg Glu Asn Phe His Arg Leu Cys 385 390 395	1199
GAA AAC TAC ATC AAG AGC TGG TTT GAG GGC CAA GGG CTG GCC GGG AAG Glu Asn Tyr Ile Lys Ser Trp Phe Glu Gly Gln Gly Leu Ala Gly Lys 400 405 410 415	1247
CTA CGG GCC ATC CAG ACG GTG TCC TGC CTC CTG CAG GGC CCA TGT GAC Leu Arg Ala Ile Gln Thr Val Ser Cys Leu Leu Gln Gly Pro Cys Asp 420 425 430	1295

GCT	GGC	AAC	CGG	GCC	TTG	GAG	CTG	AGC	GGT	GTC	ATG	GAG	AGT	GTG	ATT	1343
Ala	Gly	Asn	Arg	Ala	Leu	Glu	Leu	Ser	Gly	Val	Met	Glu	Ser	Val	Ile	
		435						440					445			
GCT	CTG	TGT	GCC	TCT	GAG	CAG	GAG	GAG	GAG	CAG	CTG	GTG	GCC	GTG	GAG	1391
Ala	Leu	Cys	Ala	Ser	Glu	Gln	Glu	Glu	Glu	Gln	Leu	Val	Ala	Val	Glu	
		450					455					460				
GCT	CTG	ATC	CAT	GCA	GCC	GGC	AAG	GCT	AAG	CGG	GCC	TCA	TTC	ATC	ACT	1439
Ala	Leu	Ile	His	Ala	Ala	Gly	Lys	Ala	Lys	Arg	Ala	Ser	Phe	Ile	Thr	
	465					470					475					
GCC	AAT	GGT	GTC	TCG	CTG	CTG	AAG	GAC	CTA	TAT	AAG	TGC	AGC	GAG	AAG	1487
Ala	Asn	Gly	Val	Ser	Leu	Leu	Lys	Asp	Leu	Tyr	Lys	Cys	Ser	Glu	Lys	
480					485				490						495	
GAC	AGC	ATC	CGC	ATC	CGG	GCG	CTA	GTG	GGA	CTC	TGT	AAG	CTC	GGT	TCG	1535
Asp	Ser	Ile	Arg	Ile	Arg	Ala	Leu	Val	Gly	Leu	Cys	Lys	Leu	Gly	Ser	
				500					505					510		
GCT	GGA	GGG	ACT	GAC	TTC	AGC	ATG	AAG	CAG	TTT	GCT	GAA	GGC	TCC	ACT	1583
Ala	Gly	Gly	Thr	Asp	Phe	Ser	Met	Lys	Gln	Phe	Ala	Glu	Gly	Ser	Thr	
			515					520					525			
CTC	AAA	CTG	GCT	AAG	CAG	TGT	CGA	AAG	TGG	CTG	TGC	AAT	GAC	CAG	ATC	1631
Leu	Lys	Leu	Ala	Lys	Gln	Cys	Arg	Lys	Trp	Leu	Cys	Asn	Asp	Gln	Ile	
		530					535					540				
GAC	GCA	GGC	ACT	CGG	GCG	TGG	GCA	GTG	GAG	GGC	CTG	GCT	TAC	CTG	ACC	1679
Asp	Ala	Gly	Thr	Arg	Arg	Trp	Ala	Val	Glu	Gly	Leu	Ala	Tyr	Leu	Thr	
	545					550					555					
TTT	GAT	GCC	GAC	GTG	AAG	GAA	GAG	TTT	GTG	GAG	GAT	GCG	GCT	GCT	CTG	1727
Phe	Asp	Ala	Asp	Val	Lys	Glu	Glu	Phe	Val	Glu	Asp	Ala	Ala	Ala	Leu	
560					565				570						575	
AAA	GCT	CTG	TTC	CAG	CTC	AGC	AGG	TTG	GAG	GAG	AGG	TCA	GTG	CTC	TTT	1775
Lys	Ala	Leu	Phe	Gln	Leu	Ser	Arg	Leu	Glu	Glu	Arg	Ser	Val	Leu	Phe	
				580					585					590		
GCG	GTG	GCC	TCA	GCG	CTG	GTG	AAC	TGC	ACC	AAC	AGC	TAT	GAC	TAC	GAG	1823
Ala	Val	Ala	Ser	Ala	Leu	Val	Asn	Cys	Thr	Asn	Ser	Tyr	Asp	Tyr	Glu	
			595					600					605			
GAG	CCC	GAC	CCC	AAG	ATG	GTG	GAG	CTG	GCC	AAG	TAT	GCC	AAG	CAG	CAT	1871
Glu	Pro	Asp	Pro	Lys	Met	Val	Glu	Leu	Ala	Lys	Tyr	Ala	Lys	Gln	His	
		610					615					620				
GTG	CCC	GAG	CAG	CAC	CCC	AAG	GAC	AAG	CCA	AGC	TTC	GTG	CGG	GCT	CGG	1919
Val	Pro	Glu	Gln	His	Pro	Lys	Asp	Lys	Pro	Ser	Phe	Val	Arg	Ala	Arg	
	625					630					635					
GTG	AAG	AAG	CTG	CTG	GCA	GCG	GGT	GTG	GTG	TCG	GCC	ATG	GTG	TGC	ATG	1967
Val	Lys	Lys	Leu	Leu	Ala	Ala	Gly	Val	Val	Ser	Ala	Met	Val	Cys	Met	
640					645					650					655	
GTG	AAG	ACG	GAG	AGC	CCT	GTG	CTG	ACC	AGT	TCC	TGC	AGA	GAG	CTG	CTC	2015
Val	Lys	Thr	Glu	Ser	Pro	Val	Leu	Thr	Ser	Ser	Cys	Arg	Glu	Leu	Leu	
				660					665					670		
TCC	AGG	GTC	TTC	TTG	GCT	TTA	GTG	GAA	GAG	GTA	GAG	GAC	CGA	GGC	ACT	2063
Ser	Arg	Val	Phe	Leu	Ala	Leu	Val	Glu	Glu	Val	Glu	Asp	Arg	Gly	Thr	
			675					680					685			
GTG	GTT	GCC	CAG	GGA	GGC	GGC	AGG	GCG	CTG	ATC	CCG	CTG	GCC	CTG	GAA	2111
Val	Val	Ala	Gln	Gly	Gly	Gly	Arg	Ala	Leu	Ile	Pro	Leu	Ala	Leu	Glu	
		690					695					700				

GGC ACC GAC GTG GGG CAG ACA AAG GCA GCC CAG GCC CTT GCC AAG CTC	2159
Gly Thr Asp Val Gly Gln Thr Lys Ala Ala Gln Ala Leu Ala Lys Leu	
705 710 715	
ACC ATC ACC TCC AAC CCG GAG ATG ACC TTC CCT GGC GAG CGG ATC TAT	2207
Thr Ile Thr Ser Asn Pro Glu Met Thr Phe Pro Gly Glu Arg Ile Tyr	
720 725 730 735	
GAG GTG GTC CGG CCC CTC GTC TCC CTG TTG CAC CTC AAC TGC TCA GGC	2255
Glu Val Val Arg Pro Leu Val Ser Leu Leu His Leu Asn Cys Ser Gly	
740 745 750	
CTG CAG AAC TTC GAG GCG CTC ATG GCC CTA ACA AAC CTG GCT GGG ATC	2303
Leu Gln Asn Phe Glu Ala Leu Met Ala Leu Thr Asn Leu Ala Gly Ile	
755 760 765	
AGC GAG AGG CTC CGG CAG AAG ATC CTG AAG GAG AAG GCT GTG CCC ATG	2351
Ser Glu Arg Leu Arg Gln Lys Ile Leu Lys Glu Lys Ala Val Pro Met	
770 775 780	
ATA GAA GGC TAC ATG TTT GAG GAG CAT GAG ATG ATC CGC CGG GCA GCC	2399
Ile Glu Gly Tyr Met Phe Glu Glu His Glu Met Ile Arg Arg Ala Ala	
785 790 795	
ACG GAG TGC ATG TGT AAC TTG GCC ATG AGC AAG GAG GTG CAG GAC CTC	2447
Thr Glu Cys Met Cys Asn Leu Ala Met Ser Lys Glu Val Gln Asp Leu	
800 805 810 815	
TTC GAA GCC CAG GGC AAT GAC CGA CTG AAG CTG CTG GTG CTG TAC AGT	2495
Phe Glu Ala Gln Gly Asn Asp Arg Leu Lys Leu Leu Val Leu Tyr Ser	
820 825 830	
GGA GAG GAT GAT GAG CTG CTA CAG CGG GCA GCT GCC GGG GGC TTG GCC	2543
Gly Glu Asp Asp Glu Leu Leu Gln Arg Ala Ala Ala Gly Gly Leu Ala	
835 840 845	
ATG CTT ACC TCC ATG CGG CCC ACG CTC TGC AGC CGC ATT CCC CAA GTG	2591
Met Leu Thr Ser Met Arg Pro Thr Leu Cys Ser Arg Ile Pro Gln Val	
850 855 860	
ACC ACA CAC TGG CTG GAG ATC CTG CAG GCC CTG CTT CTG AGC TCC AAC	2639
Thr Thr His Trp Leu Glu Ile Leu Gln Ala Leu Leu Leu Ser Ser Asn	
865 870 875	
CAG GAG CTG CAG CAC CGG GGT GCT GTG GTG GTG CTG AAC ATG GTG GAG	2687
Gln Glu Leu Gln His Arg Gly Ala Val Val Val Leu Asn Met Val Glu	
880 885 890 895	
GCC TCG AGG GAG ATT GCC AGC ACC CTG ATG GAG AGT GAG ATG ATG GAG	2735
Ala Ser Arg Glu Ile Ala Ser Thr Leu Met Glu Ser Glu Met Met Glu	
900 905 910	
ATC TTG TCA GTG CTA GCT AAG GGT GAC CAC AGC CCT GTC ACA AGG GCT	2783
Ile Leu Ser Val Leu Ala Lys Gly Asp His Ser Pro Val Thr Arg Ala	
915 920 925	
GCT GCA GCC TGC CTG GAC AAA GCA GTG GAA TAT GGG CTT ATC CAA CCC	2831
Ala Ala Ala Cys Leu Asp Lys Ala Val Glu Tyr Gly Leu Ile Gln Pro	
930 935 940	
AAC CAA GAT GGA GAG TGAGGGGGTT GTCCCTGGGC CCAAGGCTCA TGCACACGCT	2886
Asn Gln Asp Gly Glu	
945	
ACCTATTGTG GCACGGAGAG TAAGGACGGA AGCAGCTTTG GCTGGTGGTG GCTGGCATGC	2946
CCAATACTCT TGCCCATCCT CGCTTGCTGC CCTAGGATGT CCTCTGTTCT GAGTCAGCGG	3006

CCACGTTTCAG TCACACAGCC CTGCTTGGCC AGCACTGCCT GCAGCCTCAC TCAGAGGGGG 3066  
 CCTTTTTCTG TACTACTGTA GTCAGCTGGG AATGGGGAAG GTGCATCCCA ACACAGCCTG 3126  
 TGGATCCTGG GGCATTTGGA AGGGCGCACA CATCAGCAGC CTCACCAGCT GTGAGCCTGC 3186  
 TATCAGGCCT GCCCCTCCAA TAAAAGTGTG TAGAACTCC 3225

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 948 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Gln Thr Arg Pro Ala Pro Glu Thr Ala Pro Ala Arg Ala Arg Asp Thr  
 1 5 10 15  
 Leu Ser Ala Met Thr Ala Ser Ser Val Glu Gln Leu Arg Lys Glu Gly  
 20 25 30  
 Asn Glu Leu Phe Lys Cys Gly Asp Tyr Gly Gly Ala Leu Ala Ala Tyr  
 35 40 45  
 Thr Gln Ala Leu Gly Leu Asp Ala Thr Pro Gln Asp Gln Ala Val Leu  
 50 55 60  
 His Arg Asn Arg Ala Ala Cys His Leu Lys Leu Glu Asp Tyr Asp Lys  
 65 70 75 80  
 Ala Glu Thr Glu Ala Ser Lys Ala Ile Glu Lys Asp Gly Gly Asp Val  
 85 90 95  
 Lys Ala Leu Tyr Arg Arg Ser Gln Ala Leu Glu Lys Leu Gly Arg Leu  
 100 105 110  
 Asp Gln Ala Val Leu Asp Leu Gln Arg Cys Val Ser Leu Glu Pro Lys  
 115 120 125  
 Asn Lys Val Phe Gln Glu Ala Leu Arg Asn Ile Gly Gly Gln Ile Gln  
 130 135 140  
 Glu Lys Val Arg Tyr Met Ser Ser Thr Asp Ala Lys Val Glu Gln Met  
 145 150 155 160  
 Phe Gln Ile Leu Leu Asp Pro Glu Glu Lys Gly Thr Glu Lys Lys Gln  
 165 170 175  
 Lys Ala Ser Gln Asn Leu Val Val Leu Ala Arg Glu Asp Ala Gly Ala  
 180 185 190  
 Glu Lys Ile Phe Arg Ser Asn Gly Val Gln Leu Leu Gln Arg Leu Leu  
 195 200 205  
 Asp Met Gly Glu Thr Asp Leu Met Leu Ala Ala Leu Arg Thr Leu Val  
 210 215 220  
 Gly Ile Cys Ser Glu His Gln Ser Arg Thr Val Ala Thr Leu Ser Ile  
 225 230 235 240  
 Leu Gly Thr Arg Arg Val Val Ser Ile Leu Gly Val Glu Ser Gln Ala  
 245 250 255

Val Ser Leu Ala Ala Cys His Leu Leu Gln Val Met Phe Asp Ala Leu  
 260 265 270  
 Lys Glu Gly Val Lys Lys Gly Phe Arg Gly Lys Glu Gly Ala Ile Ile  
 275 280 285  
 Val Asp Pro Ala Arg Glu Leu Lys Val Leu Ile Ser Asn Leu Leu Asp  
 290 295 300  
 Leu Leu Thr Glu Val Gly Val Ser Gly Gln Gly Arg Asp Asn Ala Leu  
 305 310 315 320  
 Thr Leu Leu Ile Lys Ala Val Pro Arg Lys Ser Leu Lys Asp Pro Asn  
 325 330 335  
 Asn Ser Leu Thr Leu Trp Val Ile Asp Gln Gly Leu Lys Lys Ile Leu  
 340 345 350  
 Glu Val Gly Gly Ser Leu Gln Asp Pro Pro Gly Glu Leu Ala Val Thr  
 355 360 365  
 Ala Asn Ser Arg Met Ser Ala Ser Ile Leu Leu Ser Lys Leu Phe Asp  
 370 375 380  
 Asp Leu Lys Cys Asp Ala Glu Arg Glu Asn Phe His Arg Leu Cys Glu  
 385 390 395 400  
 Asn Tyr Ile Lys Ser Trp Phe Glu Gly Gln Gly Leu Ala Gly Lys Leu  
 405 410 415  
 Arg Ala Ile Gln Thr Val Ser Cys Leu Leu Gln Gly Pro Cys Asp Ala  
 420 425 430  
 Gly Asn Arg Ala Leu Glu Leu Ser Gly Val Met Glu Ser Val Ile Ala  
 435 440 445  
 Leu Cys Ala Ser Glu Gln Glu Glu Gln Leu Val Ala Val Glu Ala  
 450 455 460  
 Leu Ile His Ala Ala Gly Lys Ala Lys Arg Ala Ser Phe Ile Thr Ala  
 465 470 475 480  
 Asn Gly Val Ser Leu Leu Lys Asp Leu Tyr Lys Cys Ser Glu Lys Asp  
 485 490 495  
 Ser Ile Arg Ile Arg Ala Leu Val Gly Leu Cys Lys Leu Gly Ser Ala  
 500 505 510  
 Gly Gly Thr Asp Phe Ser Met Lys Gln Phe Ala Glu Gly Ser Thr Leu  
 515 520 525  
 Lys Leu Ala Lys Gln Cys Arg Lys Trp Leu Cys Asn Asp Gln Ile Asp  
 530 535 540  
 Ala Gly Thr Arg Arg Trp Ala Val Glu Gly Leu Ala Tyr Leu Thr Phe  
 545 550 555 560  
 Asp Ala Asp Val Lys Glu Glu Phe Val Glu Asp Ala Ala Ala Leu Lys  
 565 570 575  
 Ala Leu Phe Gln Leu Ser Arg Leu Glu Glu Arg Ser Val Leu Phe Ala  
 580 585 590  
 Val Ala Ser Ala Leu Val Asn Cys Thr Asn Ser Tyr Asp Tyr Glu Glu  
 595 600 605  
 Pro Asp Pro Lys Met Val Glu Leu Ala Lys Tyr Ala Lys Gln His Val

610	615	620
Pro Glu Gln His Pro Lys Asp Lys Pro Ser Phe Val Arg Ala Arg Val		
625	630	635 640
Lys Lys Leu Leu Ala Ala Gly Val Val Ser Ala Met Val Cys Met Val		
	645	650 655
Lys Thr Glu Ser Pro Val Leu Thr Ser Ser Cys Arg Glu Leu Leu Ser		
	660	665 670
Arg Val Phe Leu Ala Leu Val Glu Glu Val Glu Asp Arg Gly Thr Val		
	675	680 685
Val Ala Gln Gly Gly Gly Arg Ala Leu Ile Pro Leu Ala Leu Glu Gly		
	690	695 700
Thr Asp Val Gly Gln Thr Lys Ala Ala Gln Ala Leu Ala Lys Leu Thr		
705	710	715 720
Ile Thr Ser Asn Pro Glu Met Thr Phe Pro Gly Glu Arg Ile Tyr Glu		
	725	730 735
Val Val Arg Pro Leu Val Ser Leu Leu His Leu Asn Cys Ser Gly Leu		
	740	745 750
Gln Asn Phe Glu Ala Leu Met Ala Leu Thr Asn Leu Ala Gly Ile Ser		
	755	760 765
Glu Arg Leu Arg Gln Lys Ile Leu Lys Glu Lys Ala Val Pro Met Ile		
	770	775 780
Glu Gly Tyr Met Phe Glu Glu His Glu Met Ile Arg Arg Ala Ala Thr		
785	790	795 800
Glu Cys Met Cys Asn Leu Ala Met Ser Lys Glu Val Gln Asp Leu Phe		
	805	810 815
Glu Ala Gln Gly Asn Asp Arg Leu Lys Leu Leu Val Leu Tyr Ser Gly		
	820	825 830
Glu Asp Asp Glu Leu Leu Gln Arg Ala Ala Ala Gly Gly Leu Ala Met		
	835	840 845
Leu Thr Ser Met Arg Pro Thr Leu Cys Ser Arg Ile Pro Gln Val Thr		
	850	855 860
Thr His Trp Leu Glu Ile Leu Gln Ala Leu Leu Leu Ser Ser Asn Gln		
865	870	875 880
Glu Leu Gln His Arg Gly Ala Val Val Val Leu Asn Met Val Glu Ala		
	885	890 895
Ser Arg Glu Ile Ala Ser Thr Leu Met Glu Ser Glu Met Met Glu Ile		
	900	905 910
Leu Ser Val Leu Ala Lys Gly Asp His Ser Pro Val Thr Arg Ala Ala		
	915	920 925
Ala Ala Cys Leu Asp Lys Ala Val Glu Tyr Gly Leu Ile Gln Pro Asn		
	930	935 940
Gln Asp Gly Glu		
945		

(2) INFORMATION FOR SEQ ID NO:15:

## 1. SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6002 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: double  
 (D) TOPOLOGY: linear

11. MOLECULE TYPE: cDNA

111. HYPOTHETICAL: NO

## (x) FEATURE:

- (A) NAME/KEY: CDS  
 (B) LOCATION: 326..5092

## (x1) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```

CACGTGCATG TGTAGCATGC CTTGGTTTTT CCTTTGGCAT CTGAAAAAGG CACAACCTGA      60
AAGACCTAGA ACCCAGTGTC GGTCCCCAGG CCCTTTGGGA CAGGAAGAGA AGAGCCGTGT      120
GGCCGGGGGG AGGATGTCTT GCGGCGGGGC TGTCTCGCG GACTGACTGG ACTCCATCTC      180
CCAGCGGGCG CCGCGGCGCG GCCACGCCCC CCCACTCCCC GCGCGCGCCC GGTGGAGACT      240
TCGATTTTCA GAATTCCTCC TGGGAATGCT GACTCCTTGC TTGGTGCCCT GATGCTTCTC      300
TGAGATAAAC TGATGAATTG GAACC ATG GTG CAA AAG AAG AAG TTC TGT CCT      352
                        Met Val Gln Lys Lys Lys Phe Cys Pro
                        1                               5

CGG TTA CTT GAC TAT CTA GTG ATC GTA GGG GCC AGG CAC CCG AGC AGT      400
Arg Leu Leu Asp Tyr Leu Val Ile Val Gly Ala Arg His Pro Ser Ser
 10                        15                        20                        25

GAT AGC GTG GCC CAG ACT CCT GAA TTG CTA CGG CGA TAC CCC TTG GAG      448
Asp Ser Val Ala Gln Thr Pro Glu Leu Leu Arg Arg Tyr Pro Leu Glu
                        30                        35                        40

GAT CAC ACT GAG TTT CCC CTG CCC CCA GAT GTA GTG TTC TTC TGC CAG      496
Asp His Thr Glu Phe Pro Leu Pro Pro Asp Val Val Phe Phe Cys Gln
                        45                        50                        55

CCC GAG GGC TGC CTG AGC GTG CGG CAG CGG CGC ATG AGC CTT CGG GAT      544
Pro Glu Gly Cys Leu Ser Val Arg Gln Arg Arg Met Ser Leu Arg Asp
 60                        65                        70

GAT ACC TCT TTT GTC TTC ACC CTC ACT GAC AAG GAC ACT GGA GTC ACG      592
Asp Thr Ser Phe Val Phe Thr Leu Thr Asp Lys Asp Thr Gly Val Thr
 75                        80                        85

CGA TAT GGC ATC TGT GTT AAC TTC TAC CGC TCC TTC CAA AAG CGA ATC      640
Arg Tyr Gly Ile Cys Val Asn Phe Tyr Arg Ser Phe Gln Lys Arg Ile
 90                        95                        100                        105

TCT AAG GAG AAG GGG GAA GGT GGG GCA GGG TCC CGT GGG AAG GAA GGA      688
Ser Lys Glu Lys Gly Glu Gly Gly Ala Gly Ser Arg Gly Lys Glu Gly
 110                        115                        120

ACC CAT GCC ACC TGT GCC TCA GAA GAG GGT GGC ACT GAG AGC TCA GAG      736
Thr His Ala Thr Cys Ala Ser Glu Glu Gly Gly Thr Glu Ser Ser Glu
 125                        130                        135

AGT GGC TCA TCC CTG CAG CCT CTC AGT GCT GAC TCT ACC CCT GAT GTG      784
Ser Gly Ser Ser Leu Gln Pro Leu Ser Ala Asp Ser Thr Pro Asp Val
 140                        145                        150

```

AAC Asn 155	CAG Gln	TCT Ser	CCT Pro	CGG Arg	GGC Gly	AAA Lys 160	CGC Arg	CGG Arg	GCC Ala	AAG Lys 165	GGG Ala 165	AGC Gly	CGC Ser	TCC Arg	TCC Ser	832
CGC Arg 170	AAC Asn	AGT Ser	ACT Thr	CTC Leu	ACG Thr 175	TCC Ser	CTG Leu	TGC Cys	GTG Val 180	CTC Leu 180	AGC Ser	CAC His	TAC Tyr	CCT Pro	TTC Phe 185	880
TTC Phe	TCC Ser	ACC Thr	TTC Phe	CGA Arg 190	GAG Glu	TGT Cys	TTG Leu	TAT Tyr 195	ACT Thr 195	CTC Leu	AAG Lys	CGC Arg	CTG Leu	GTG Val 200	GAC Asp	928
TGC Cys	TGT Cys	AGT Ser	GAG Glu 205	CGC Arg	CTT Leu	CTG Leu	GGC Gly	AAG Lys 210	AAA Lys	CTG Leu	GGC Gly	ATC Ile	CCT Pro 215	CGA Arg	GGC Gly	976
GTA Val	CAA Gln 220	AGG Arg	GAC Asp	ACC Thr	ATG Met	TGG Trp	CGG Arg 225	ATC Ile	TTT Phe	ACT Thr	GGA Gly	TCG Ser 230	CTG Leu	CTG Leu	GTA Val	1024
GAG Glu 235	GAG Glu	AAG Lys	TCA Ser	AGT Ser	GCC Ala	CTT Leu 240	CTG Leu	CAT His	GAC Asp	CTT Leu	CGA Arg 245	GAG Glu	ATT Ile	GAG Glu	GCC Ala	1072
TGG Trp 250	ATC Ile	TAT Tyr	CGA Arg	TTG Leu	CTG Leu 255	CGC Arg	TCC Ser	CCA Pro	GTA Val	CCC Pro 260	GTC Val	TCT Ser	GGG Gly	CAG Gln	AAG Lys 265	1120
CGA Arg	GTA Val	GAC Asp	ATC Ile	GAG Glu 270	GTC Val	CTA Leu	CCC Pro	CAA Gln	GAG Glu 275	CTC Leu	CAG Gln	CCA Pro	GCT Ala	CTG Leu 280	ACC Thr	1168
TTT Phe	GCT Ala	CTT Leu	CCA Pro 285	GAC Asp	CCA Pro	TCT Ser	CGA Arg	TTC Phe 290	ACC Thr	CTA Leu	GTG Val	GAT Asp	TTC Phe 295	CCA Pro	CTG Leu	1216
CAC His	CTT Leu	CCC Pro 300	TTG Leu	GAA Glu	CTT Leu	CTA Leu	GGT Gly 305	GTG Val	GAC Asp	GCC Ala	TGT Cys 310	CTC Leu	CAG Gln	GTG Val	CTA Leu	1264
ACC Thr	TGC Cys 315	ATT Ile	CTG Leu	TTA Leu	GAG Glu	CAC His 320	AAG Lys	GTG Val	GTG Val	CTA Leu	CAG Gln 325	TCC Ser	CGA Arg	GAC Asp	TAC Tyr	1312
AAT Asn 330	GCA Ala	CTC Leu	TCC Ser	ATG Met	TCT Ser 335	GTG Val	ATG Met	GCA Ala	TTC Phe	GTG Val 340	GCA Ala	ATG Met	ATC Ile	TAC Tyr	CCA Pro 345	1360
CTG Leu	GAA Glu	TAT Tyr	ATG Met	TTT Phe 350	CCT Pro	GTC Val	ATC Ile	CCG Pro	CTG Leu 355	CTA Leu	CCC Pro	ACC Thr	TGC Cys	ATG Met	GCA Ala 360	1408
TCA Ser	GCA Ala	GAG Glu	CAG Gln 365	CTG Leu	CTG Leu	TTG Leu	GCT Ala	CCA Pro 370	ACC Thr	CCG Pro	TAC Tyr	ATC Ile	ATT Ile 375	GGG Gly	GTT Val	1456
CCT Pro	GCC Ala	AGC Ser 380	TTC Phe	TTC Phe	CTC Leu	TAC Tyr	AAA Lys 385	CTG Leu	GAC Asp	TTC Phe	AAA Lys 390	ATG Met	CCT Pro	GAT Asp	GAT Asp	1504
GTA Val	TGG Trp 395	CTA Leu	GTG Val	GAT Asp	CTG Leu	GAC Asp 400	AGC Ser	AAT Asn	AGG Arg	GTG Val	ATT Ile 405	GCC Ala	CCC Pro	ACC Thr	AAT Asn	1552
GCA Ala 410	GAA Glu	GTG Val	CTG Leu	CCT Pro	ATC Ile 415	CTG Leu	CCA Pro	GAA Glu	CCA Pro	GAA Glu 420	TCA Ser	CTA Leu	GAG Glu	CTG Leu	AAA Lys 425	1600



AAG CAT TTA AAG CAG GCC TTG GCC AGC ATG AGT CTC AAC ACC CAG CCC Lys His Leu Lys Gln Ala Leu Ala Ser Met Ser Leu Asn Thr Gln Pro 430 435 440	1648
ATC CTC AAT CTG GAG AAA TTT CAT GAG GGC CAG GAG ATC CCC CTT CTC Ile Leu Asn Leu Glu Lys Phe His Glu Gly Gln Glu Ile Pro Leu Leu 445 450 455	1696
TTG GGA AGG CCT TCT AAT GAC CTG CAG TCC ACA CCG TCC ACT GAA TTC Leu Gly Arg Pro Ser Asn Asp Leu Gln Ser Thr Pro Ser Thr Glu Phe 460 465 470	1744
AAC CCA CTC ATC TAT GGC AAT GAT GTG GAT TCT GTG GAT GTT GCA ACC Asn Pro Leu Ile Tyr Gly Asn Asp Val Asp Ser Val Asp Val Ala Thr 475 480 485	1792
AGG GTT GCC ATG GTA CGG TTC TTC AAT TCC GCC AAC GTG CTG CAG GGA Arg Val Ala Met Val Arg Phe Phe Asn Ser Ala Asn Val Leu Gln Gly 490 495 500 505	1840
TTT CAG ATG CAC ACG CGT ACC CTG CGC CTC TTT CCT CGG CCT GTG GTA Phe Gln Met His Thr Arg Thr Leu Arg Leu Phe Pro Arg Pro Val Val 510 515 520	1888
GCT TTT CAA GCT GGC TCC TTT CTA GCC TCA CGT CCC CGG CAG ACT CCT Ala Phe Gln Ala Gly Ser Phe Leu Ala Ser Arg Pro Arg Gln Thr Pro 525 530 535	1936
TTT GCC GAG AAA TTG GCC AGG ACT CAG GCT GTG GAG TAC TTT GGG GAA Phe Ala Glu Lys Leu Ala Arg Thr Gln Ala Val Glu Tyr Phe Gly Glu 540 545 550	1984
TGG ATC CTT AAC CCC ACC AAC TAT GCC TTT CAG CGA ATT CAC AAC AAT Trp Ile Leu Asn Pro Thr Asn Tyr Ala Phe Gln Arg Ile His Asn Asn 555 560 565	2032
ATG TTT GAT CCA GCC CTG ATT GGT GAC AAG CCA AAG TGG TAT GCT CAT Met Phe Asp Pro Ala Leu Ile Gly Asp Lys Pro Lys Trp Tyr Ala His 570 575 580 585	2080
CAG CTG CAG CCT ATC CAC TAT CGC GTC TAT GAC AGC AAT TCC CAG CTG Gln Leu Gln Pro Ile His Tyr Arg Val Tyr Asp Ser Asn Ser Gln Leu 590 595 600	2128
GCT GAG GCC CTG AGT GTA CCA CCA GAG CGG GAC TCT GAC TCC GAA CCT Ala Glu Ala Leu Ser Val Pro Pro Glu Arg Asp Ser Asp Ser Glu Pro 605 610 615	2176
ACT GAT GAT AGT GGC AGT GAT AGT ATG GAT TAT GAC GAT TCA AGC TCT Thr Asp Asp Ser Gly Ser Asp Ser Met Asp Tyr Asp Asp Ser Ser Ser 620 625 630	2224
TCT TAC TCC TCC CTT GGT GAC TTT GTC AGT GAA ATG ATG AAA TGT GAC Ser Tyr Ser Ser Leu Gly Asp Phe Val Ser Glu Met Met Lys Cys Asp 635 640 645	2272
ATT AAT GGT GAT ACT CCC AAT GTG GAC CCT CTG ACA CAT GCA GCA CTG Ile Asn Gly Asp Thr Pro Asn Val Asp Pro Leu Thr His Ala Ala Leu 650 655 660 665	2320
GGG GAT GCC AGC GAG GTG GAG ATT GAC GAG CTG CAG AAT CAG AAG GAA Gly Asp Ala Ser Glu Val Glu Ile Asp Glu Leu Gln Asn Gln Lys Glu 670 675 680	2368
GCA GAA GAG CCT GGC CCA GAC AGT GAG AAC TCT CAG GAA AAC CCC CCA Ala Glu Glu Pro Gly Pro Asp Ser Glu Asn Ser Gln Glu Asn Pro Pro 685 690 695	2416

CTG	CGC	TCC	AGC	TCT	AGC	ACC	ACA	GCC	AGC	AGC	AGC	CCC	AGC	ACT	GTC	2464
Leu	Arg	Ser	Ser	Ser	Ser	Thr	Thr	Ala	Ser	Ser	Ser	Pro	Ser	Thr	Val	
		700					705					710				
ATC	CAC	GGA	GCC	AAC	TCT	GAA	CCT	GCT	GAC	TCT	ACG	GAG	ATG	GAT	GAT	2512
Ile	His	Gly	Ala	Asn	Ser	Glu	Pro	Ala	Asp	Ser	Thr	Glu	Met	Asp	Asp	
	715					720				725						
AAG	GCA	GCA	GTA	GGC	GTC	TCC	AAG	CCC	CTC	CCT	TCC	GTG	CCT	CCC	AGC	2560
Lys	Ala	Ala	Val	Gly	Val	Ser	Lys	Pro	Leu	Pro	Ser	Val	Pro	Pro	Ser	
	730				735					740					745	
ATT	GGC	AAA	TCG	AAC	ATG	GAC	AGA	CGT	CAG	GCA	GAA	ATT	GGA	GAG	GGG	2608
Ile	Gly	Lys	Ser	Asn	Met	Asp	Arg	Arg	Gln	Ala	Glu	Ile	Gly	Glu	Gly	
			750						755						760	
TCA	GTG	CGC	CGG	CGA	ATC	TAT	GAC	AAT	CCA	TAC	TTC	GAG	CCC	CAA	TAT	2656
Ser	Val	Arg	Arg	Arg	Ile	Tyr	Asp	Asn	Pro	Tyr	Phe	Glu	Pro	Gln	Tyr	
			765					770						775		
GGC	TTT	CCC	CCT	GAG	GAA	GAT	GAG	GAT	GAG	CAG	GGG	GAA	AGT	TAC	ACT	2704
Gly	Phe	Pro	Pro	Glu	Glu	Asp	Glu	Asp	Glu	Gln	Gly		Ser	Tyr	Thr	
		780					785					790				
CCC	CGA	TTC	AGC	CAA	CAT	GTC	AGT	GGC	AAT	CGG	GCT	CAA	AAG	CTG	CTG	2752
Pro	Arg	Phe	Ser	Gln	His	Val	Ser	Gly	Asn	Arg	Ala	Gln	Lys	Leu	Leu	
		795				800					805					
CGG	CCC	AAC	AGC	TTG	AGA	CTG	GCA	AGT	GAC	TCA	GAT	GCA	GAG	TCA	GAC	2800
Arg	Pro	Asn	Ser	Leu	Arg	Leu	Ala	Ser	Asp	Ser	Asp	Ala	Glu	Ser	Asp	
	810				815					820					825	
TCT	CGG	GCA	AGC	TCT	CCC	AAC	TCC	ACC	GTC	TCC	AAC	ACC	AGC	ACC	GAG	2848
Ser	Arg	Ala	Ser	Ser	Pro	Asn	Ser	Thr	Val	Ser	Asn	Thr	Ser	Thr	Glu	
				830					835						840	
GGC	TTC	GGG	GGC	ATC	ATG	TCT	TTT	GCC	AGC	AGC	CTC	TAT	CGG	AAC	CAC	2896
Gly	Phe	Gly	Gly	Ile	Met	Ser	Phe	Ala	Ser	Ser	Leu	Tyr	Arg	Asn	His	
			845					850					855			
AGT	ACC	AGC	TTC	AGT	CTT	TCA	AAC	CTC	ACA	CTG	CCC	ACC	AAA	GGT	GCC	2944
Ser	Thr	Ser	Phe	Ser	Leu	Ser	Asn	Leu	Thr	Leu	Pro	Thr	Lys	Gly	Ala	
		860					865					870				
CGA	GAG	AAG	GCC	ACG	CCC	TTC	CCC	AGT	CTG	AAA	GGA	AAC	AGG	AGG	GCG	2992
Arg	Glu	Lys	Ala	Thr	Pro	Phe	Pro	Ser	Leu	Lys		Asn	Arg	Arg	Ala	
		875				880					885					
TTA	GTG	GAT	CAG	AAG	TCA	TCT	GTC	ATT	AAA	CAC	AGC	CCA	ACA	GTG	AAA	3040
Leu	Val	Asp	Gln	Lys	Ser	Ser	Val	Ile	Lys	His	Ser	Pro	Thr	Val	Lys	
		890			895				900						905	
AGA	GAA	CCT	CCA	TCA	CCC	CAG	GGT	CGA	TCC	AGC	AAT	TCT	AGT	GAG	AAC	3088
Arg	Glu	Pro	Pro	Ser	Pro	Gln	Gly	Arg	Ser	Ser	Asn	Ser	Ser	Glu	Asn	
				910					915					920		
CAG	CAG	TTC	CTG	AAG	GAG	GTG	GTG	CAC	AGC	GTG	CTG	GAC	GGC	CAG	GGA	3136
Gln	Gln	Phe	Leu	Lys	Glu	Val	Val	His	Ser	Val	Leu	Asp	Gly	Gln	Gly	
			925					930					935			
GTT	GGC	TGG	CTC	AAC	ATG	AAA	AAG	GTG	CGC	CGG	CTG	CTG	GAG	AGC	GAG	3184
Val	Gly	Trp	Leu	Asn	Met	Lys	Lys	Val	Arg	Arg	Leu	Leu	Glu	Ser	Glu	
		940					945					950				
CAG	CTG	CGA	GTC	TTT	GTC	CTG	AGC	AAG	CTG	AAC	CGC	ATG	GTG	CAG	TCA	3232
Gln	Leu	Arg	Val	Phe	Val	Leu	Ser	Lys	Leu	Asn	Arg	Met	Val	Gln	Ser	
		955				960					965					

GAG GAC GAT GCC CGG CAG GAC ATC ATC CGG GAT GTG GAG ATC AGT CGG Glu Asp Asp Ala Arg Gln Asp Ile Ile Pro Asp Val Glu Ile Ser Arg 970 975 980 985	3280
AAG GTG TAC AAG GGA ATG TTA GAC CTC CTC AAG TGT ACA GTC CTC AGC Lys Val Tyr Lys Gly Met Leu Asp Leu Leu Lys Cys Thr Val Leu Ser 990 995 1000	3328
TTG GAG CAG TCC TAT GCC CAC GCG GGT CTG GGT GGC ATG GCC AGC ATC Leu Glu Gln Ser Tyr Ala His Ala Gly Leu Gly Gly Met Ala Ser Ile 1005 1010 1015	3376
TTT GGG CTT TTG GAG ATT GCC CAG ACC CAC TAC TAT AGT AAA GAA CCA Phe Gly Leu Leu Glu Ile Ala Gln Thr His Tyr Tyr Ser Lys Glu Pro 1020 1025 1030	3424
GAC AAG CGG AAG AGA AGT CCA ACA GAA AGT GTA AAT ACC CCA GTT GGC Asp Lys Arg Lys Arg Ser Pro Thr Glu Ser Val Asn Thr Pro Val Gly 1035 1040 1045	3472
AAG GAT CCT GGC CTA GCT GGG CGG GGG GAC CCA AAG GCT ATG GCA CAA Lys Asp Pro Gly Leu Ala Gly Arg Gly Asp Pro Lys Ala Met Ala Gln 1050 1055 1060 1065	3520
CTG AGA GTT CCA CAA CTG GGA CCT CGG GCA CCA AGT GCC ACA GGA AAG Leu Arg Val Pro Gln Leu Gly Pro Arg Ala Pro Ser Ala Thr Gly Lys 1070 1075 1080	3568
GGT CCT AAG GAA CTG GAC ACC AGA AGT TTA AAG GAA GAA AAT TTT ATA Gly Pro Lys Glu Leu Asp Thr Arg Ser Leu Lys Glu Glu Asn Phe Ile 1085 1090 1095	3616
GCA TCT ATT GGG CCT GAA GTA ATC AAA CCT GTC TTT GAC CTT GGT GAG Ala Ser Ile Gly Pro Glu Val Ile Lys Pro Val Phe Asp Leu Gly Glu 1100 1105 1110	3664
ACA GAG GAG AAA AAG TCC CAG ATC AGC GCA GAC AGT GGT GTG AGC CTG Thr Glu Glu Lys Lys Ser Gln Ile Ser Ala Asp Ser Gly Val Ser Leu 1115 1120 1125	3712
ACG TCT AGT TCC CAG AGG ACT GAT CAA GAC TCT GTC ATC GGC GTG AGT Thr Ser Ser Ser Gln Arg Thr Asp Gln Asp Ser Val Ile Gly Val Ser 1130 1135 1140 1145	3760
CCA GCT GTT ATG ATC CGC AGC TCA AGT CAG GAT TCT GAA GTT AGC ACC Pro Ala Val Met Ile Arg Ser Ser Ser Gln Asp Ser Glu Val Ser Thr 1150 1155 1160	3808
GTG GTG AGT AAT AGC TCT GGA GAG ACC CTT GGA GCT GAC AGT GAC TTG Val Val Ser Asn Ser Ser Gly Glu Thr Leu Gly Ala Asp Ser Asp Leu 1165 1170 1175	3856
AGC AGC AAT GCA GGT GAT GGA CCA GGT GGC GAG GGC AGT GTT CAC CTG Ser Ser Asn Ala Gly Asp Gly Pro Gly Gly Glu Gly Ser Val His Leu 1180 1185 1190	3904
GCA AGC TCT CGG GGC ACT TTG TCT GAT AGT GAA ATT GAG ACC AAC TCT Ala Ser Ser Arg Gly Thr Leu Ser Asp Ser Glu Ile Glu Thr Asn Ser 1195 1200 1205	3952
GCC ACA AGC ACC ATC TTT GGT AAA GCC CAC AGC TTG AAG CCA AGC ATA Ala Thr Ser Thr Ile Phe Gly Lys Ala His Ser Leu Lys Pro Ser Ile 1210 1215 1220 1225	4000
AAG GAG AAG CTG GCA GGC AGC CCC ATT CGT ACT TCT GAA GAT GTG AGC Lys Glu Lys Leu Ala Gly Ser Pro Ile Arg Thr Ser Glu Asp Val Ser 1230 1235 1240	4048

CAG CGA GTC TAT CTC TAT GAG GGA CTC CTA GGC AAA GAG CGT TCT ACT Gln Arg Val Tyr Leu Tyr Glu Gly Leu Leu Gly Lys Glu Arg Ser Thr 1245 1250 1255	4096
TTA TGG GAC CAA ATG CAA TTC TGG GAA GAT GCC TTC TTA GAT GCT GTG Leu Trp Asp Gln Met Gln Phe Trp Glu Asp Ala Phe Leu Asp Ala Val 1260 1265 1270	4144
ATG TTG GAG AGA GAA GGG ATG GGT ATG GAC CAG GGT CCC CAG GAA ATG Met Leu Glu Arg Glu Gly Met Gly Met Asp Gln Gly Pro Gln Glu Met 1275 1280 1285	4192
ATC GAC AGG TAC CTG TCC CTT GGA GAA CAT GAC CGG AAG CGC CTG GAA Ile Asp Arg Tyr Leu Ser Leu Gly Glu His Asp Arg Lys Arg Leu Glu 1290 1295 1300 1305	4240
GAT GAT GAA GAT CGC TTG CTG GCC ACA CTT CTG CAC AAC CTC ATC TCC Asp Asp Glu Asp Arg Leu Leu Ala Thr Leu Leu His Asn Leu Ile Ser 1310 1315 1320	4288
TAC ATG CTG CTG ATG AAG GTA AAT AAG AAT GAC ATC CGC AAG AAG GTG Tyr Met Leu Leu Met Lys Val Asn Lys Asn Asp Ile Arg Lys Lys Val 1325 1330 1335	4336
AGG CGC CTA ATG GGA AAG TCG CAC ATT GGG CTT GTG TAC AGC CAG CAA Arg Arg Leu Met Gly Lys Ser His Ile Gly Leu Val Tyr Ser Gln Gln 1340 1345 1350	4384
ATC AAT GAG GTG CTT GAT CAG CTG GCG AAC CTG AAT GGA CGC GAT CTC Ile Asn Glu Val Leu Asp Gln Leu Ala Asn Leu Asn Gly Arg Asp Leu 1355 1360 1365	4432
TCT ATC TGG TCC AGT GGC AGC CGG CAC ATG AAG AAG CAG ACA TTT GTG Ser Ile Trp Ser Ser Gly Ser Arg His Met Lys Lys Gln Thr Phe Val 1370 1375 1380 1385	4480
GTA CAT GCA GGG ACA GAT ACA AAC GGA GAT ATC TTT TTC ATG GAG GTG Val His Ala Gly Thr Asp Thr Asn Gly Asp Ile Phe Phe Met Glu Val 1390 1395 1400	4528
TGC GAT GAC TGT GTG GTG TTG CGT AGT AAC ATC GGA ACA GTG TAT GAG Cys Asp Asp Cys Val Val Leu Arg Ser Asn Ile Gly Thr Val Tyr Glu 1405 1410 1415	4576
CGC TGG TGG TAC GAG AAG CTC ATC AAC ATG ACC TAC TGT CCC AAG ACG Arg Trp Trp Tyr Glu Lys Leu Ile Asn Met Thr Tyr Cys Pro Lys Thr 1420 1425 1430	4624
AAG GTG TTG TGC TTG TGG CGT AGA AAT GGC TCT GAG ACC CAG CTC AAC Lys Val Leu Cys Leu Trp Arg Arg Asn Gly Ser Glu Thr Gln Leu Asn 1435 1440 1445	4672
AAG TTC TAT ACT AAA AAG TGT CGG GAG CTG TAC TAC TGT GTG AAG GAC Lys Phe Tyr Thr Lys Lys Cys Arg Glu Leu Tyr Tyr Cys Val Lys Asp 1450 1455 1460 1465	4720
AGC ATG GAG CGC GCT GCC GCC CGA CAG CAA AGC ATC AAA CCC GGA CCT Ser Met Glu Arg Ala Ala Ala Arg Gln Gln Ser Ile Lys Pro Gly Pro 1470 1475 1480	4768
GAA TTG GGT GGC GAG TTC CCT GTG CAG GAC CTG AAG ACT GGT GAG GGT Glu Leu Gly Gly Glu Phe Pro Val Gln Asp Leu Lys Thr Gly Glu Gly 1485 1490 1495	4816
GGC CTG CTG CAG GTG ACC CTG GAA GGG ATC AAC CTC AAA TTC ATG CAC Gly Leu Leu Gln Val Thr Leu Glu Gly Ile Asn Leu Lys Phe Met His 1500 1505 1510	4864

AAT CAG GTT TTC ATA GAG CTG AAT CAC ATT AAA AAG TCC AAT ACA GTT Asn Gln Val Phe Ile Glu Leu Asn His Ile Lys Lys Cys Asn Thr Val 1515 1520 1525	4912
CGA GGC GTC TTT GTC CTG GAG GAA TTT GTT CCT GAA ATT AAA GAA GTG Arg Gly Val Phe Val Leu Glu Glu Phe Val Pro Glu Ile Lys Glu Val 1530 1535 1540 1545	4960
GTG AGC CAC AAG TAC AAG ACA CCA ATG GCC CAC GAA ATC TGC TAC TCC Val Ser His Lys Tyr Lys Thr Pro Met Ala His Glu Ile Cys Tyr Ser 1550 1555 1560	5008
GTA TTA TGT CTC TTC TCG TAC GTG GCT GCA GTT CAT AGC AGT GAG GAA Val Leu Cys Leu Phe Ser Tyr Val Ala Ala Val His Ser Ser Glu Glu 1565 1570 1575	5056
GAT CTC AGA ACC CCG CCC CGG CCT GTC TCT AGC TGA TGGAGAGGGG Asp Leu Arg Thr Pro Pro Arg Pro Val Ser Ser *	5102
1580 1585	
CTACGCAGCT GCCCCAGCCC AGGGCACGCC CCTGGCCCCT TGCTGTTCCC AAGTGCACGA	5162
TGCTGCTGTG ACTGAGGAGT GGATGATGCT CGTGTGTCT CTGCAAGCCC CCTGCTGTGG	5222
CTTGTTGGT TACCGTTAT GTGTCCCTCT GAGTGTGTCT TGAGCGTGTG CACCTTCTCC	5282
CTCTCCACTC CCAGAAGACC AAAGTGCCTT CCCCTCAGGG CTCAAGAATG TGTACAGTCT	5342
GTGGGGCCGG TGTGAACCCA CTATTTTGTG TCCTTGAGAC ATTTGTGTTG TGGTTCCTTG	5402
TCCTTGTTCCC TGGCGTTATA ACTGTCCACT GCAAGAGTCT GGCTCTCCCT TCTCTGTGAC	5462
CCGGCATGAC TGGGCGCCTG GAGCAGTTTC ACTCTGTGAG GAGTGAGGGA ACCCTGGGGC	5522
TCACCCCTCTC AGAGGAAGGG CACAGAGAGG AAGGGAAGAA TTGGGGGGCA GCCGGAGTGA	5582
GTGGCAGCCT CCCTGCTTCC TTCTGCATTC CCAAGCCGGC AGCTACTGCC CAGGGCCCCG	5642
AGTGTGGCT GCTGCCTGCC ACAGCCTCTG TGAAGTGCAGT GGAGCGGCGA ATTCCCTGTG	5702
GCCTGCCACG CCTTCGGCAT CAGAGGATGG AGTGGTCGAG GCTAGTGGAG TCCCAGGGAC	5762
CGCTGGCTGC TCTGCCTGAG CATCAGGGAG GGGGCAGGAA AGACCAAGCT GGGTTTGCAC	5822
ATCTGTCTGC AGGCTGTCTC TCCAGGCACG GGGTGTGAGG AGGGAGAGAC AGCCTGGGTA	5882
TGGGCAAGAA ATGACTGTAA ATATTTTCAGC CCCACATTAT TTATAGAAAA TGTACAGTTG	5942
TGTGAATGTG AAATAAATGT CCTCAACTCC CAAAAAAAAA AAAAAAAAAA AAAAAAAAAA	6002

## (2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1589 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met	Val	Gln	Lys	Lys	Lys	Phe	Cys	Pro	Arg	Leu	Leu	Asp	Tyr	Leu	Val
1				5					10					15	
Ile	Val	Gly	Ala	Arg	His	Pro	Ser	Ser	Asp	Ser	Val	Ala	Gln	Thr	Pro

20					25					30					
Glu	Leu	Leu	Arg	Arg	Tyr	Pro	Leu	Glu	Asp	His	Thr	Glu	Phe	Pro	Leu
	35						40					45			
Pro	Pro	Asp	Val	Val	Phe	Phe	Cys	Gln	Pro	Glu	Gly	Cys	Leu	Ser	Val
	50					55					60				
Arg	Gln	Arg	Arg	Met	Ser	Leu	Arg	Asp	Asp	Thr	Ser	Phe	Val	Phe	Thr
65					70					75					80
Leu	Thr	Asp	Lys	Asp	Thr	Gly	Val	Thr	Arg	Tyr	Gly	Ile	Cys	Val	Asn
				85					90					95	
Phe	Tyr	Arg	Ser	Phe	Gln	Lys	Arg	Ile	Ser	Lys	Glu	Lys	Gly	Glu	Gly
			100					105					110		
Gly	Ala	Gly	Ser	Arg	Gly	Lys	Glu	Gly	Thr	His	Ala	Thr	Cys	Ala	Ser
		115					120					125			
Glu	Glu	Gly	Gly	Thr	Glu	Ser	Ser	Glu	Ser	Gly	Ser	Ser	Leu	Gln	Pro
	130					135					140				
Leu	Ser	Ala	Asp	Ser	Thr	Pro	Asp	Val	Asn	Gln	Ser	Pro	Arg	Gly	Lys
145					150					155					160
Arg	Arg	Ala	Lys	Ala	Gly	Ser	Arg	Ser	Arg	Asn	Ser	Thr	Leu	Thr	Ser
				165					170						175
Leu	Cys	Val	Leu	Ser	His	Tyr	Pro	Phe	Phe	Ser	Thr	Phe	Arg	Glu	Cys
			180					185					190		
Leu	Tyr	Thr	Leu	Lys	Arg	Leu	Val	Asp	Cys	Cys	Ser	Glu	Arg	Leu	Leu
		195					200					205			
Gly	Lys	Lys	Leu	Gly	Ile	Pro	Arg	Gly	Val	Gln	Arg	Asp	Thr	Met	Trp
	210					215					220				
Arg	Ile	Phe	Thr	Gly	Ser	Leu	Leu	Val	Glu	Glu	Lys	Ser	Ser	Ala	Leu
225					230					235					240
Leu	His	Asp	Leu	Arg	Glu	Ile	Glu	Ala	Trp	Ile	Tyr	Arg	Leu	Leu	Arg
				245					250					255	
Ser	Pro	Val	Pro	Val	Ser	Gly	Gln	Lys	Arg	Val	Asp	Ile	Glu	Val	Leu
			260					265					270		
Pro	Gln	Glu	Leu	Gln	Pro	Ala	Leu	Thr	Phe	Ala	Leu	Pro	Asp	Pro	Ser
		275					280					285			
Arg	Phe	Thr	Leu	Val	Asp	Phe	Pro	Leu	His	Leu	Pro	Leu	Glu	Leu	Leu
	290					295					300				
Gly	Val	Asp	Ala	Cys	Leu	Gln	Val	Leu	Thr	Cys	Ile	Leu	Leu	Glu	His
305					310					315					320
Lys	Val	Val	Leu	Gln	Ser	Arg	Asp	Tyr	Asn	Ala	Leu	Ser	Met	Ser	Val
				325					330					335	
Met	Ala	Phe	Val	Ala	Met	Ile	Tyr	Pro	Leu	Glu	Tyr	Met	Phe	Pro	Val
			340					345					350		
Ile	Pro	Leu	Leu	Pro	Thr	Cys	Met	Ala	Ser	Ala	Glu	Gln	Leu	Leu	Leu
		355					360					365			
Ala	Pro	Thr	Pro	Tyr	Ile	Ile	Gly	Val	Pro	Ala	Ser	Phe	Phe	Leu	Tyr
						375					380				

Lys Leu Asp Phe Lys Met Pro Asp Asp Val Trp Leu Val Asp Leu Asp  
 385 390 395 400  
 Ser Asn Arg Val Ile Ala Pro Thr Asn Ala Glu Val Leu Pro Ile Leu  
 405 410 415  
 Pro Glu Pro Glu Ser Leu Glu Leu Lys Lys His Leu Lys Gln Ala Leu  
 420 425 430  
 Ala Ser Met Ser Leu Asn Thr Gln Pro Ile Leu Asn Leu Glu Lys Phe  
 435 440 445  
 His Glu Gly Gln Glu Ile Pro Leu Leu Leu Gly Arg Pro Ser Asn Asp  
 450 455 460  
 Leu Gln Ser Thr Pro Ser Thr Glu Phe Asn Pro Leu Ile Tyr Gly Asn  
 465 470 475 480  
 Asp Val Asp Ser Val Asp Val Ala Thr Arg Val Ala Met Val Arg Phe  
 485 490 495  
 Phe Asn Ser Ala Asn Val Leu Gln Gly Phe Gln Met His Thr Arg Thr  
 500 505 510  
 Leu Arg Leu Phe Pro Arg Pro Val Val Ala Phe Gln Ala Gly Ser Phe  
 515 520 525  
 Leu Ala Ser Arg Pro Arg Gln Thr Pro Phe Ala Glu Lys Leu Ala Arg  
 530 535 540  
 Thr Gln Ala Val Glu Tyr Phe Gly Glu Trp Ile Leu Asn Pro Thr Asn  
 545 550 555 560  
 Tyr Ala Phe Gln Arg Ile His Asn Asn Met Phe Asp Pro Ala Leu Ile  
 565 570 575  
 Gly Asp Lys Pro Lys Trp Tyr Ala His Gln Leu Gln Pro Ile His Tyr  
 580 585 590  
 Arg Val Tyr Asp Ser Asn Ser Gln Leu Ala Glu Ala Leu Ser Val Pro  
 595 600 605  
 Pro Glu Arg Asp Ser Asp Ser Glu Pro Thr Asp Asp Ser Gly Ser Asp  
 610 615 620  
 Ser Met Asp Tyr Asp Asp Ser Ser Ser Ser Tyr Ser Ser Leu Gly Asp  
 625 630 635 640  
 Phe Val Ser Glu Met Met Lys Cys Asp Ile Asn Gly Asp Thr Pro Asn  
 645 650 655  
 Val Asp Pro Leu Thr His Ala Ala Leu Gly Asp Ala Ser Glu Val Glu  
 660 665 670  
 Ile Asp Glu Leu Gln Asn Gln Lys Glu Ala Glu Glu Pro Gly Pro Asp  
 675 680 685  
 Ser Glu Asn Ser Gln Glu Asn Pro Pro Leu Arg Ser Ser Ser Ser Thr  
 690 695 700  
 Thr Ala Ser Ser Ser Pro Ser Thr Val Ile His Gly Ala Asn Ser Glu  
 705 710 715 720  
 Pro Ala Asp Ser Thr Glu Met Asp Asp Lys Ala Ala Val Gly Val Ser  
 725 730 735  
 Lys Pro Leu Pro Ser Val Pro Pro Ser Ile Gly Lys Ser Asn Met Asp

740					745					750					
Arg	Arg	Gln	Ala	Glu	Ile	Gly	Glu	Gly	Ser	Val	Arg	Arg	Arg	Ile	Tyr
		755					760					765			
Asp	Asn	Pro	Tyr	Phe	Glu	Pro	Gln	Tyr	Gly	Phe	Pro	Pro	Glu	Glu	Asp
	770					775					780				
Glu	Asp	Glu	Gln	Gly	Glu	Ser	Tyr	Thr	Pro	Arg	Phe	Ser	Gln	His	Val
785					790					795				800	
Ser	Gly	Asn	Arg	Ala	Gln	Lys	Leu	Leu	Arg	Pro	Asn	Ser	Leu	Arg	Leu
				805					810					815	
Ala	Ser	Asp	Ser	Asp	Ala	Glu	Ser	Asp	Ser	Arg	Ala	Ser	Ser	Pro	Asn
			820					825					830		
Ser	Thr	Val	Ser	Asn	Thr	Ser	Thr	Glu	Gly	Phe	Gly	Gly	Ile	Met	Ser
		835					840					845			
Phe	Ala	Ser	Ser	Leu	Tyr	Arg	Asn	His	Ser	Thr	Ser	Phe	Ser	Leu	Ser
	850					855					860				
Asn	Leu	Thr	Leu	Pro	Thr	Lys	Gly	Ala	Arg	Glu	Lys	Ala	Thr	Pro	Phe
865					870					875					880
Pro	Ser	Leu	Lys	Gly	Asn	Arg	Arg	Ala	Leu	Val	Asp	Gln	Lys	Ser	Ser
				885					890					895	
Val	Ile	Lys	His	Ser	Pro	Thr	Val	Lys	Arg	Glu	Pro	Pro	Ser	Pro	Gln
			900					905					910		
Gly	Arg	Ser	Ser	Asn	Ser	Ser	Glu	Asn	Gln	Gln	Phe	Leu	Lys	Glu	Val
		915					920					925			
Val	His	Ser	Val	Leu	Asp	Gly	Gln	Gly	Val	Gly	Trp	Leu	Asn	Met	Lys
	930					935					940				
Lys	Val	Arg	Arg	Leu	Leu	Glu	Ser	Glu	Gln	Leu	Arg	Val	Phe	Val	Leu
945					950					955					960
Ser	Lys	Leu	Asn	Arg	Met	Val	Gln	Ser	Glu	Asp	Asp	Ala	Arg	Gln	Asp
			965						970					975	
Ile	Ile	Pro	Asp	Val	Glu	Ile	Ser	Arg	Lys	Val	Tyr	Lys	Gly	Met	Leu
			980					985					990		
Asp	Leu	Leu	Lys	Cys	Thr	Val	Leu	Ser	Leu	Glu	Gln	Ser	Tyr	Ala	His
		995					1000					1005			
Ala	Gly	Leu	Gly	Gly	Met	Ala	Ser	Ile	Phe	Gly	Leu	Leu	Glu	Ile	Ala
	1010					1015					1020				
Gln	Thr	His	Tyr	Tyr	Ser	Lys	Glu	Pro	Asp	Lys	Arg	Lys	Arg	Ser	Pro
1025					1030					1035					1040
Thr	Glu	Ser	Val	Asn	Thr	Pro	Val	Gly	Lys	Asp	Pro	Gly	Leu	Ala	Gly
				1045					1050					1055	
Arg	Gly	Asp	Pro	Lys	Ala	Met	Ala	Gln	Leu	Arg	Val	Pro	Gln	Leu	Gly
			1060					1065					1070		
Pro	Arg	Ala	Pro	Ser	Ala	Thr	Gly	Lys	Gly	Pro	Lys	Glu	Leu	Asp	Thr
		1075					1080					1085			
Arg	Ser	Leu	Lys	Glu	Glu	Asn	Phe	Ile	Ala	Ser	Ile	Gly	Pro	Glu	Val
		1090				1095					1100				



Ile Lys Pro Val Phe Asp Leu Gly Glu Thr Glu Glu Lys Lys Ser Gln  
 1105 1110 1115 1120  
 Ile Ser Ala Asp Ser Gly Val Ser Leu Thr Ser Ser Ser Gln Arg Thr  
 1125 1130 1135  
 Asp Gln Asp Ser Val Ile Gly Val Ser Pro Ala Val Met Ile Arg Ser  
 1140 1145 1150  
 Ser Ser Gln Asp Ser Glu Val Ser Thr Val Val Ser Asn Ser Ser Gly  
 1155 1160 1165  
 Glu Thr Leu Gly Ala Asp Ser Asp Leu Ser Ser Asn Ala Gly Asp Gly  
 1170 1175 1180  
 Pro Gly Gly Glu Gly Ser Val His Leu Ala Ser Ser Arg Gly Thr Leu  
 1185 1190 1195 1200  
 Ser Asp Ser Glu Ile Glu Thr Asn Ser Ala Thr Ser Thr Ile Phe Gly  
 1205 1210 1215  
 Lys Ala His Ser Leu Lys Pro Ser Ile Lys Glu Lys Leu Ala Gly Ser  
 1220 1225 1230  
 Pro Ile Arg Thr Ser Glu Asp Val Ser Gln Arg Val Tyr Leu Tyr Glu  
 1235 1240 1245  
 Gly Leu Leu Gly Lys Glu Arg Ser Thr Leu Trp Asp Gln Met Gln Phe  
 1250 1255 1260  
 Trp Glu Asp Ala Phe Leu Asp Ala Val Met Leu Glu Arg Glu Gly Met  
 1265 1270 1275 1280  
 Gly Met Asp Gln Gly Pro Gln Glu Met Ile Asp Arg Tyr Leu Ser Leu  
 1285 1290 1295  
 Gly Glu His Asp Arg Lys Arg Leu Glu Asp Asp Glu Asp Arg Leu Leu  
 1300 1305 1310  
 Ala Thr Leu Leu His Asn Leu Ile Ser Tyr Met Leu Leu Met Lys Val  
 1315 1320 1325  
 Asn Lys Asn Asp Ile Arg Lys Lys Val Arg Arg Leu Met Gly Lys Ser  
 1330 1335 1340  
 His Ile Gly Leu Val Tyr Ser Gln Gln Ile Asn Glu Val Leu Asp Gln  
 1345 1350 1355 1360  
 Leu Ala Asn Leu Asn Gly Arg Asp Leu Ser Ile Trp Ser Ser Gly Ser  
 1365 1370 1375  
 Arg His Met Lys Lys Gln Thr Phe Val Val His Ala Gly Thr Asp Thr  
 1380 1385 1390  
 Asn Gly Asp Ile Phe Phe Met Glu Val Cys Asp Asp Cys Val Val Leu  
 1395 1400 1405  
 Arg Ser Asn Ile Gly Thr Val Tyr Glu Arg Trp Trp Tyr Glu Lys Leu  
 1410 1415 1420  
 Ile Asn Met Thr Tyr Cys Pro Lys Thr Lys Val Leu Cys Leu Trp Arg  
 1425 1430 1435 1440  
 Arg Asn Gly Ser Glu Thr Gln Leu Asn Lys Phe Tyr Thr Lys Lys Cys  
 1445 1450 1455  
 Arg Glu Leu Tyr Tyr Cys Val Lys Asp Ser Met Glu Arg Ala Ala Ala

1460                      1465                      1470  
 Arg Gln Gln Ser Ile Lys Pro Gly Pro Glu Leu Gly Gly Glu Phe Pro  
       1475                      1480                      1485  
 Val Gln Asp Leu Lys Thr Gly Glu Gly Gly Leu Leu Gln Val Thr Leu  
       1490                      1495                      1500  
 Glu Gly Ile Asn Leu Lys Phe Met His Asn Gln Val Phe Ile Glu Leu  
 1505                      1510                      1515                      1520  
 Asn His Ile Lys Lys Cys Asn Thr Val Arg Gly Val Phe Val Leu Glu  
                          1525                      1530                      1535  
 Glu Phe Val Pro Glu Ile Lys Glu Val Val Ser His Lys Tyr Lys Thr  
                          1540                      1545                      1550  
 Pro Met Ala His Glu Ile Cys Tyr Ser Val Leu Cys Leu Phe Ser Tyr  
                          1555                      1560                      1565  
 Val Ala Ala Val His Ser Ser Glu Glu Asp Leu Arg Thr Pro Pro Arg  
                          1570                      1575                      1580  
 Pro Val Ser Ser \*  
 1585

## (2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2473 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

- (ix) FEATURE:
- (A) NAME/KEY: CDS
  - (B) LOCATION: 14..2404

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CCGACGAGGA GACATGGCGG CGGCGCCGGT AGCGGCTGGG TCTGGAGCCG GCCGAGGGAG	60
ACGGTCGGCA GCCACAGTGG CGGCTTGGGG CGGATGGGGC GGCCGGCCGC GGCCTGGTAA	120
CATTCTGCTG CAGCTGCGGC AGGGCCAGCT GACCGGCCGG GGCCTGGTCC GGGCGGTGCA	180
GTTCACTGAG ACTTTTTTGA CGGAGAGGGA CAAACAATCC AAGTGGAGTG GAATTCCTCA	240
GCTGCTCCTC AAGCTGCACA CCACCAGCCA CCTCCACAGT GACTTTGTTG AGTGTCAAAA	300
CATCCTCAAG GAAATTTCTC CTCTTCTCTC CATGGAGGCT ATGGCATTG TTAAGTGAAGA	360
GAGGAAACTT ACCCAAGAAA CCACTTATCC AAATACTTAC ATTTTGGACT TGTGTTGGAGG	420
TGTTGATCTT CTGTAGAAA TTCTTATGAG GCCTACGATC TCTATCCGGG GACAGAAACT	480
GAAAATAAGT GATGAAATGT CCAAGGACTG CTTGAGTATC CTGTATAATA CCTGTGTCTG	540
TACAGAGGGA GTTACAAAGC GTTTGGCAGA AAAGAATGAC TTTGTGATCT TCCTGTTTAC	600
ATTGATGACA AGTAAGAAGA CATTCTTACA AACAGCAACC CTCATTGAAG ATATTTTAGG	660

TSTTAAAAAS	GAAATGATCC	GACTAGATGA	AGTCCCCAAT	CTGAGTTCCT	TAGTATCCAA	720
TTTCGATCAG	CAGCAGCTCG	CTAATTTCTG	CCGGATTCTG	GCTGTCACCA	TTTCAGAGAT	780
GGATACAGGG	AATGATGACA	AGCACACGCT	TCTTGCCAAA	AATGCTCAAC	AGAAGAAGAG	840
CTTGAGTTTG	GGGCTTTCTG	CAGCTGAAAT	CAATCAAGCG	GGCCTTCTCA	GCATTCCTGG	900
CTTTGTTGAG	CGGCTTTTGA	AACTGGCGAC	TGGAAAGGTG	TCAGAGTCAA	CGGGCACAGC	960
CAGCTTCCTT	CAGGAGTTGG	AAGAGTGGTA	CACATGGCTA	GACAATGCTT	TGGTGCTAGA	1020
TSCCCTGATG	CGAGTGGCCA	ATGAGGAGTC	AGAGCACAAAT	CAAGCCTCCA	TTGTGTTCCC	1080
TCCTCCAGGG	GCTTCTGAGG	AGAATGGCCT	GCCTCACACG	TCAGCCAGAA	CCCAGCTGCC	1140
CCAGTCAATG	AAGATTATGC	ATGAGATCAT	GTACAAACTG	GAAGTGCTCT	ATGTCCTCTG	1200
CGTGCTGCTG	ATGGGGCGTC	AGCGAAACCA	GGTTCACAGA	ATGATTGCAG	AGTTCAAGCT	1260
GATCCCTGGA	CTTAATAATT	TGTTTGACAA	ACTGATTGG	AGGAAGCATT	CAGCATCTGC	1320
CCTTGTCCTC	CATGGTCACA	ACCAGAACTG	TGACTGTAGC	CCGGACATCA	CCTTGAAGAT	1380
ACAGTTTTTG	AGGCTTCTTC	AGAGCTTCAG	TGACCACCAC	GAGAACAAGT	ACTTGTTACT	1440
CAACAACCAG	GAGCTGAATG	AACTCAGTGC	CATCTCTCTC	AAGGCCAACA	TCCCTGAGGT	1500
GGAAGCTGTC	CTCAACACCG	ACAGGAGTTT	GGTGTGTGAT	GGGAAGAGGG	GCTTATTAAC	1560
TCGTCTGCTG	CAGGTCATGA	AGAAGGAGCC	AGCAGAGTCG	TCTTTCAGGT	TTTGGCAAGC	1620
TCGGGCTGTG	GAGAGTTTCC	TCCGAGGGAC	CACCTCCTAT	GCAGACCAGA	TGTTCTTGCT	1680
GAAGCGAGGC	CTCTTGAGGC	ACATCCTTTA	CTGCATTGTG	GACAGCGAGT	GTAAGTCAAG	1740
GGATGTGCTC	CAGAGTTACT	TTGACCTCCT	GGGGGAGCTG	ATGAAGTTCA	ACGTTGATGC	1800
ATTCAAGAGA	TTCAATAAAA	ATATCAACAC	CGATGCAAAG	TTCCAGGTAT	TCCTGAAGCA	1860
GATCAACAGC	TCCCTGGTGG	ACTCCAACAT	GCTGGTGCGC	TGTGTCACTC	TGTCCCTGGA	1920
CCGATTTGAA	AACCAGGTGG	ATATGAAAGT	TGCCGAGGTA	CTGTCTGAAT	GCCGCCTGCT	1980
CGCCTACATA	TCCCAGGTGC	CCACGCAGAT	GTCCTTCCTC	TTCCGCCTCA	TCAACATCAT	2040
CCACGTGCAG	ACGCTGACCC	AGGAGAACGT	CAGCTGCCTC	AACACCAGCC	TGGTGATCCT	2100
GATGCTGGCC	CGACGAAAAG	AGCGGCTGCC	CCTGTACCTG	CGGCTGCTGC	AGCGGATGGA	2160
GCACAGCAAG	AAGTACCCCG	GCTTCCTGCT	CAACAACTTC	CACAACCTGC	TGCGCTTCTG	2220
GCAGCAGCAC	TACCTGCACA	AGGACAAGGA	CAGCACCTGC	CTAGAGAACA	GCTCCTGCAT	2280
CAGCTTCTCA	TACTGGAAGG	AGACAGTGTC	CATCCTGTTG	AACCCGGACC	GGCAGTCACC	2340
CTCTGCTCTC	GTTAGCTACA	TTGAGGAGCC	CTACATGGAC	ATAGACAGGG	ACTTCACTGA	2400
GGAGTGACCT	TGGGCCAGGC	CTCGGGAGGC	TGCTGGGCCA	GTGTGGGTGA	GCGTGGGTAC	2460
GATGCCACAC	GCC					2473

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 797 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:  
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```

Met Ala Ala Ala Pro Val Ala Ala Gly Ser Gly Ala Gly Arg Gly Arg
1           5           10           15
Arg Ser Ala Ala Thr Val Ala Ala Trp Gly Gly Trp Gly Gly Arg Pro
          20           25           30
Arg Pro Gly Asn Ile Leu Leu Gln Leu Arg Gln Gly Gln Leu Thr Gly
          35           40           45
Arg Gly Leu Val Arg Ala Val Gln Phe Thr Glu Thr Phe Leu Thr Glu
          50           55           60
Arg Asp Lys Gln Ser Lys Trp Ser Gly Ile Pro Gln Leu Leu Leu Lys
          65           70           75           80
Leu His Thr Thr Ser His Leu His Ser Asp Phe Val Glu Cys Gln Asn
          85           90           95
Ile Leu Lys Glu Ile Ser Pro Leu Leu Ser Met Glu Ala Met Ala Phe
          100          105          110
Val Thr Glu Glu Arg Lys Leu Thr Gln Glu Thr Thr Tyr Pro Asn Thr
          115          120          125
Tyr Ile Phe Asp Leu Phe Gly Gly Val Asp Leu Leu Val Glu Ile Leu
          130          135          140
Met Arg Pro Thr Ile Ser Ile Arg Gly Gln Lys Leu Lys Ile Ser Asp
          145          150          155          160
Glu Met Ser Lys Asp Cys Leu Ser Ile Leu Tyr Asn Thr Cys Val Cys
          165          170          175
Thr Glu Gly Val Thr Lys Arg Leu Ala Glu Lys Asn Asp Phe Val Ile
          180          185          190
Phe Leu Phe Thr Leu Met Thr Ser Lys Lys Thr Phe Leu Gln Thr Ala
          195          200          205
Thr Leu Ile Glu Asp Ile Leu Gly Val Lys Lys Glu Met Ile Arg Leu
          210          215          220
Asp Glu Val Pro Asn Leu Ser Ser Leu Val Ser Asn Phe Asp Gln Gln
          225          230          235          240
Gln Leu Ala Asn Phe Cys Arg Ile Leu Ala Val Thr Ile Ser Glu Met
          245          250          255
Asp Thr Gly Asn Asp Asp Lys His Thr Leu Leu Ala Lys Asn Ala Gln
          260          265          270
Gln Lys Lys Ser Leu Ser Leu Gly Pro Ser Ala Ala Glu Ile Asn Gln
          275          280          285
Ala Ala Leu Leu Ser Ile Pro Gly Phe Val Glu Arg Leu Cys Lys Leu
          290          295          300

```

Ala Thr Arg Lys Val Ser Glu Ser Thr Gly Thr Ala Ser Phe Leu Gln  
 305 310 315 320  
 Glu Leu Glu Glu Trp Tyr Thr Trp Leu Asp Asn Ala Leu Val Leu Asp  
 325 330 335  
 Ala Leu Met Arg Val Ala Asn Glu Glu Ser Glu His Asn Gln Ala Ser  
 340 345 350  
 Ile Val Phe Pro Pro Pro Gly Ala Ser Glu Glu Asn Gly Leu Pro His  
 355 360 365  
 Thr Ser Ala Arg Thr Gln Leu Pro Gln Ser Met Lys Ile Met His Glu  
 370 375 380  
 Ile Met Tyr Lys Leu Glu Val Leu Tyr Val Leu Cys Val Leu Leu Met  
 385 390 395 400  
 Gly Arg Gln Arg Asn Gln Val His Arg Met Ile Ala Glu Phe Lys Leu  
 405 410 415  
 Ile Pro Gly Leu Asn Asn Leu Phe Asp Lys Leu Ile Trp Arg Lys His  
 420 425 430  
 Ser Ala Ser Ala Leu Val Leu His Gly His Asn Gln Asn Cys Asp Cys  
 435 440 445  
 Ser Pro Asp Ile Thr Leu Lys Ile Gln Phe Leu Arg Leu Leu Gln Ser  
 450 455 460  
 Phe Ser Asp His His Glu Asn Lys Tyr Leu Leu Leu Asn Asn Gln Glu  
 465 470 475 480  
 Leu Asn Glu Leu Ser Ala Ile Ser Leu Lys Ala Asn Ile Pro Glu Val  
 485 490 495  
 Glu Ala Val Leu Asn Thr Asp Arg Ser Leu Val Cys Asp Gly Lys Arg  
 500 505 510  
 Gly Leu Leu Thr Arg Leu Leu Gln Val Met Lys Lys Glu Pro Ala Glu  
 515 520 525  
 Ser Ser Phe Arg Phe Trp Gln Ala Arg Ala Val Glu Ser Phe Leu Arg  
 530 535 540  
 Gly Thr Thr Ser Tyr Ala Asp Gln Met Phe Leu Leu Lys Arg Gly Leu  
 545 550 555 560  
 Leu Glu His Ile Leu Tyr Cys Ile Val Asp Ser Glu Cys Lys Ser Arg  
 565 570 575  
 Asp Val Leu Gln Ser Tyr Phe Asp Leu Leu Gly Glu Leu Met Lys Phe  
 580 585 590  
 Asn Val Asp Ala Phe Lys Arg Phe Asn Lys Asn Ile Asn Thr Asp Ala  
 595 600 605  
 Lys Phe Gln Val Phe Leu Lys Gln Ile Asn Ser Ser Leu Val Asp Ser  
 610 615 620  
 Asn Met Leu Val Arg Cys Val Thr Leu Ser Leu Asp Arg Phe Glu Asn  
 625 630 635 640  
 Gln Val Asp Met Lys Val Ala Glu Val Leu Ser Glu Cys Arg Leu Leu  
 645 650 655  
 Ala Tyr Ile Ser Gln Val Pro Thr Gln Met Ser Phe Leu Phe Arg Leu

660							665					670				
Ile	Asn	Ile	Ile	His	Val	Gln	Thr	Leu	Thr	Gln	Glu	Asn	Val	Ser	Cys	
		675					680					685				
Leu	Asn	Thr	Ser	Leu	Val	Ile	Leu	Met	Leu	Ala	Arg	Arg	Lys	Glu	Arg	
	690					695					700					
Leu	Pro	Leu	Tyr	Leu	Arg	Leu	Leu	Gln	Arg	Met	Glu	His	Ser	Lys	Lys	
705					710					715					720	
Tyr	Pro	Gly	Phe	Leu	Leu	Asn	Asn	Phe	His	Asn	Leu	Leu	Arg	Phe	Trp	
			725						730					735		
Gln	Gln	His	Tyr	Leu	His	Lys	Asp	Lys	Asp	Ser	Thr	Cys	Leu	Glu	Asn	
			740					745					750			
Ser	Ser	Cys	Ile	Ser	Phe	Ser	Tyr	Trp	Lys	Glu	Thr	Val	Ser	Ile	Leu	
		755					760					765				
Leu	Asn	Pro	Asp	Arg	Gln	Ser	Pro	Ser	Ala	Leu	Val	Ser	Tyr	Ile	Glu	
	770					775					780					
Glu	Pro	Tyr	Met	Asp	Ile	Asp	Arg	Asp	Phe	Thr	Glu	Glu				
785					790					795						

CLAIMS

What is claimed is:

1. A composition comprising an isolated polynucleotide encoding a protein having TNF-R1-DD ligand protein activity

5           2. The composition of claim 1 wherein said polynucleotide is selected from the group consisting of:

          (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 2 to nucleotide 1231;

          (b) a polynucleotide comprising a fragment of the nucleotide  
10           sequence of SEQ ID NO:1;

          (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2;

          (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:2; and

15           (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

3. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:

20           (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 2 to nucleotide 415;

          (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:3;

          (c) a polynucleotide encoding an TNF-R1-DD ligand protein  
25           comprising the amino acid sequence of SEQ ID NO:4;

          (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:4; and

          (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

30

4. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence
5. A host cell transformed with a composition of claim 4.
6. The host cell of claim 5, wherein said cell is a mammalian cell.
7. A process for producing an TNF-R1-DD ligand protein, which comprises:
- (a) growing a culture of the host cell of claim 5 in a suitable culture medium; and
- (b) purifying the TNF-R1-DD ligand protein from the culture.
8. A composition comprising a protein having TNF-R1-DD ligand protein activity.
9. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:2; and
- (b) fragments of the amino acid sequence of SEQ ID NO:2;
- said protein being substantially free from other mammalian proteins.
10. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:4; and
- (b) fragments of the amino acid sequence of SEQ ID NO:4;
- said protein being substantially free from other mammalian proteins.
11. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:6; and
- (b) fragments of the amino acid sequence of SEQ ID NO:6;



said protein being substantially free from other mammalian proteins.

12. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

5

13. A composition comprising an antibody which specifically reacts with the TNF-R1-DD ligand protein of claim 8.

14. A method of identifying an inhibitor of TNF-R death domain binding which comprises:

(a) combining an TNF-R death domain protein with a composition of claim 8, said combination forming a first binding mixture;

(b) measuring the amount of binding between the TNF-R death domain protein and the TNF-R1-DD ligand protein in the first binding mixture;

15

(c) combining a compound with the TNF-R death domain protein and an TNF-R1-DD ligand protein to form a second binding mixture;

(d) measuring the amount of binding in the second binding mixture; and

(e) comparing the amount of binding in the first binding mixture with the amount of binding in the second binding mixture;

20

wherein the compound is capable of inhibiting TNF-R death domain binding when a decrease in the amount of binding of the second binding mixture occurs.

15. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:

25

(a) the amino acid sequence of SEQ ID NO:2;

(b) fragments of the amino acid sequence of SEQ ID NO:2;

(c) the amino acid sequence of SEQ ID NO:4;

- (d) fragments of the amino acid sequence of SEQ ID NO:4;
- (e) the amino acid sequence of SEQ ID NO:6;
- (f) fragments of the amino acid sequence of SEQ ID NO:6;
- (g) the amino acid sequence of SEQ ID NO:8; and
- 5 (h) fragments of the amino acid sequence of SEQ ID NO:8.

16. A method of preventing or ameliorating an inflammatory condition which comprises administering a therapeutically effective amount of a composition of claim 12.

10

17. TNF-R1-DD ligand protein produced according to the method of claim 7.

18. A method of inhibiting TNF-R death domain binding comprising  
15 administering a therapeutically effective amount of a composition of claim 12.

19. A method of preventing or ameliorating an inflammatory condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a pharmaceutically acceptable carrier and a  
20 protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

20. A method of inhibiting TNF-R death domain binding comprising administering to a mammalian subject a therapeutically effective amount of a  
25 composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

21. A composition comprising an inhibitor identified according to the  
30 method of claim 14.

22. The composition of claim 21 further comprising a pharmaceutically acceptable carrier.

23. A method of preventing or ameliorating an inflammatory condition comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

24. A method of inhibiting TNF-R death domain binding comprising administering to a mammalian subject a therapeutically effective amount of the composition of claim 22.

25. A composition comprising a pharmaceutically acceptable carrier and a protein selected from the group consisting of IGFBP-5 and fragments thereof having TNF-R1-DD ligand protein activity.

26. A method of identifying an inhibitor of TNF-R death domain binding which comprises:

(a) transforming a cell with a first polynucleotide encoding an TNF-R death domain protein, a second polynucleotide encoding an TNF-R1-DD ligand protein, and at least one reporter gene, wherein the expression of the reporter gene is regulated by the binding of the TNF-R1-DD ligand protein encoded by the second polynucleotide to the TNF-R death domain protein encoded by the first polynucleotide;

(b) growing the cell in the presence of and in the absence of a compound; and

(c) comparing the degree of expression of the reporter gene in the presence of and in the absence of the compound;

wherein the compound is capable of inhibiting TNF-R death domain binding when a decrease in the degree of expression of the reporter gene occurs.

27. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 2 to nucleotide 1231;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:1, which encodes a protein having TNF-R1-DD  
5 ligand protein activity;

(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:2;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 and  
10 having TNF-R1-DD ligand protein activity;

(e) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 2 to nucleotide 415;

(f) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:3, which encodes a protein having TNF-R1-DD  
15 ligand protein activity;

(g) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:4;

(h) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 and  
20 having TNF-R1-DD ligand protein activity;

(i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 2 to nucleotide 559;

(j) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:5, which encodes a protein having TNF-R1-DD  
25 ligand protein activity;

(k) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:6;

(l) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 and  
30 having TNF-R1-DD ligand protein activity;

(m) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 57 to nucleotide 875;

(n) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:7, which encodes a protein having TNF-R1-DD ligand protein activity;

5 (o) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:8;

(p) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 and having TNF-R1-DD ligand protein activity; and

10 (q) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(p), which encodes a protein having TNF-R1-DD ligand protein activity.

28. The method of claim 26 wherein the cell is a yeast cell.

15 29. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 2 to nucleotide 931;

20 (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:9;

(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:10; and

25 (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

30. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:

30 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 2 to nucleotide 1822;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:11;

(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12;

5 (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:12; and

(e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

10 31. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10; and

(b) fragments of the amino acid sequence of SEQ ID NO:10;  
said protein being substantially free from other mammalian proteins.

15

32. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12; and

(b) fragments of the amino acid sequence of SEQ ID NO:12;  
20 said protein being substantially free from other mammalian proteins.

33. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:

25 (a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10;

(c) the amino acid sequence of SEQ ID NO:12; and

(d) fragments of the amino acid sequence of SEQ ID NO:12.

30 34. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 2 to nucleotide 931;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:9, which encodes a protein having TNF-R1-DD ligand protein activity;

5 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:10;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 and having TNF-R1-DD ligand protein activity;

10 (e) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 2 to nucleotide 1822;

(f) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:11, which encodes a protein having TNF-R1-DD ligand protein activity;

15 (g) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:12; and

(h) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 and having TNF-R1-DD ligand protein activity; and

20 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), which encodes a protein having TNF-R1-DD ligand protein activity.

35. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:

25 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 3 to nucleotide 2846;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:13;

30 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:14; and

(e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

36. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14; and
  - (b) fragments of the amino acid sequence of SEQ ID NO:14;
- said protein being substantially free from other mammalian proteins.

37. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14; and
- (b) fragments of the amino acid sequence of SEQ ID NO:14.

38. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 3 to nucleotide 2846;
- (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:13, which encodes a protein having TNF-R1-DD ligand protein activity;
- (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:14;
- (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 and having TNF-R1-DD ligand protein activity; and
- (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d), which encodes a protein having TNF-R1-DD ligand protein activity.

39. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:



(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 326 to nucleotide 5092;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:15;

5 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:16; and

10 (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

40. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16; and

15 (b) fragments of the amino acid sequence of SEQ ID NO:16;  
said protein being substantially free from other mammalian proteins.

41. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:

20 (a) the amino acid sequence of SEQ ID NO:16; and

(b) fragments of the amino acid sequence of SEQ ID NO:16.

42. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:

25 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 326 to nucleotide 5092;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:15, which encodes a protein having TNF-R1-DD ligand protein activity;

30 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:16;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 and having TNF-R1-DD ligand protein activity; and

5 (e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d), which encodes a protein having TNF-R1-DD ligand protein activity.

43. The composition of claim 1 wherein said polynucleotide sequence is selected from the group consisting of:

10 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 14 to nucleotide 2404;

(b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:17;

15 (c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18;

(d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:18; and

(e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d).

20

44. The composition of claim 8 wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18; and

(b) fragments of the amino acid sequence of SEQ ID NO:18;

25 said protein being substantially free from other mammalian proteins.

45. The method of claim 14 wherein said TNF-R1-DD ligand protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18; and

30 (b) fragments of the amino acid sequence of SEQ ID NO:18.

46. The method of claim 26 wherein the second polynucleotide is selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 14 to nucleotide 2404;

5 (b) a polynucleotide comprising a fragment of the nucleotide sequence of SEQ ID NO:17, which encodes a protein having TNF-R1-DD ligand protein activity;

(c) a polynucleotide encoding an TNF-R1-DD ligand protein comprising the amino acid sequence of SEQ ID NO:18;

10 (d) a polynucleotide encoding an TNF-R1-DD ligand protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 and having TNF-R1-DD ligand protein activity; and

(e) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(d), which  
15 encodes a protein having TNF-R1-DD ligand protein activity.

Fig. 1

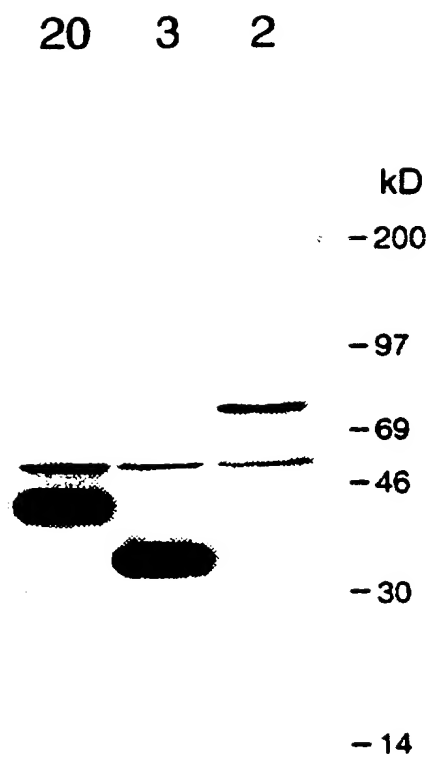


Fig. 2

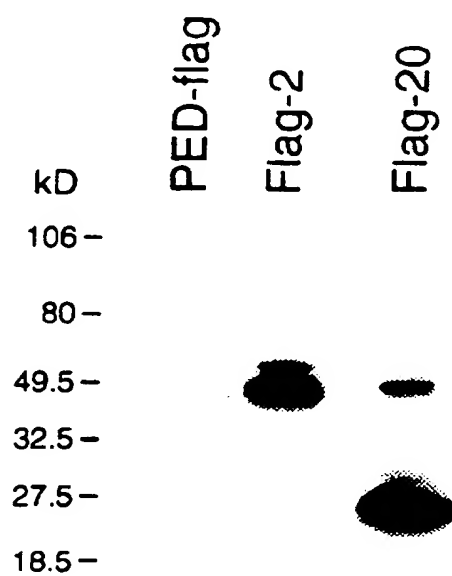


Fig. 3A

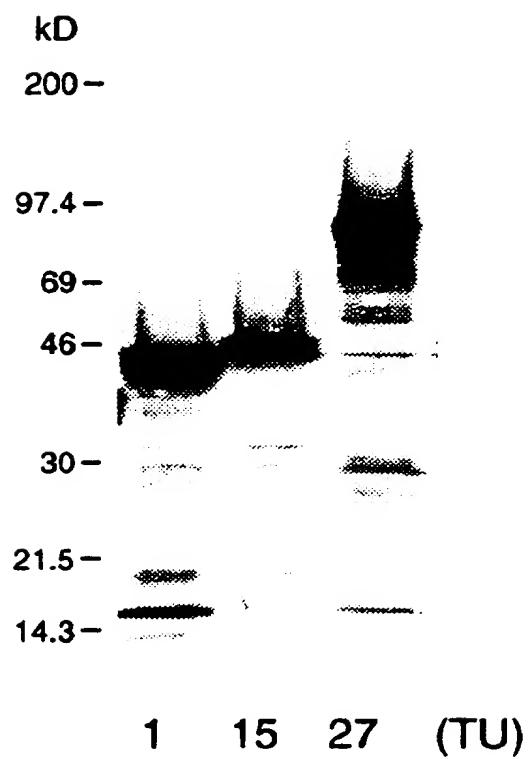


Fig. 3B

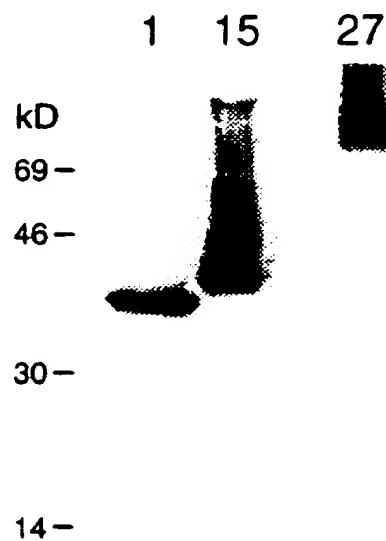


Fig. 4

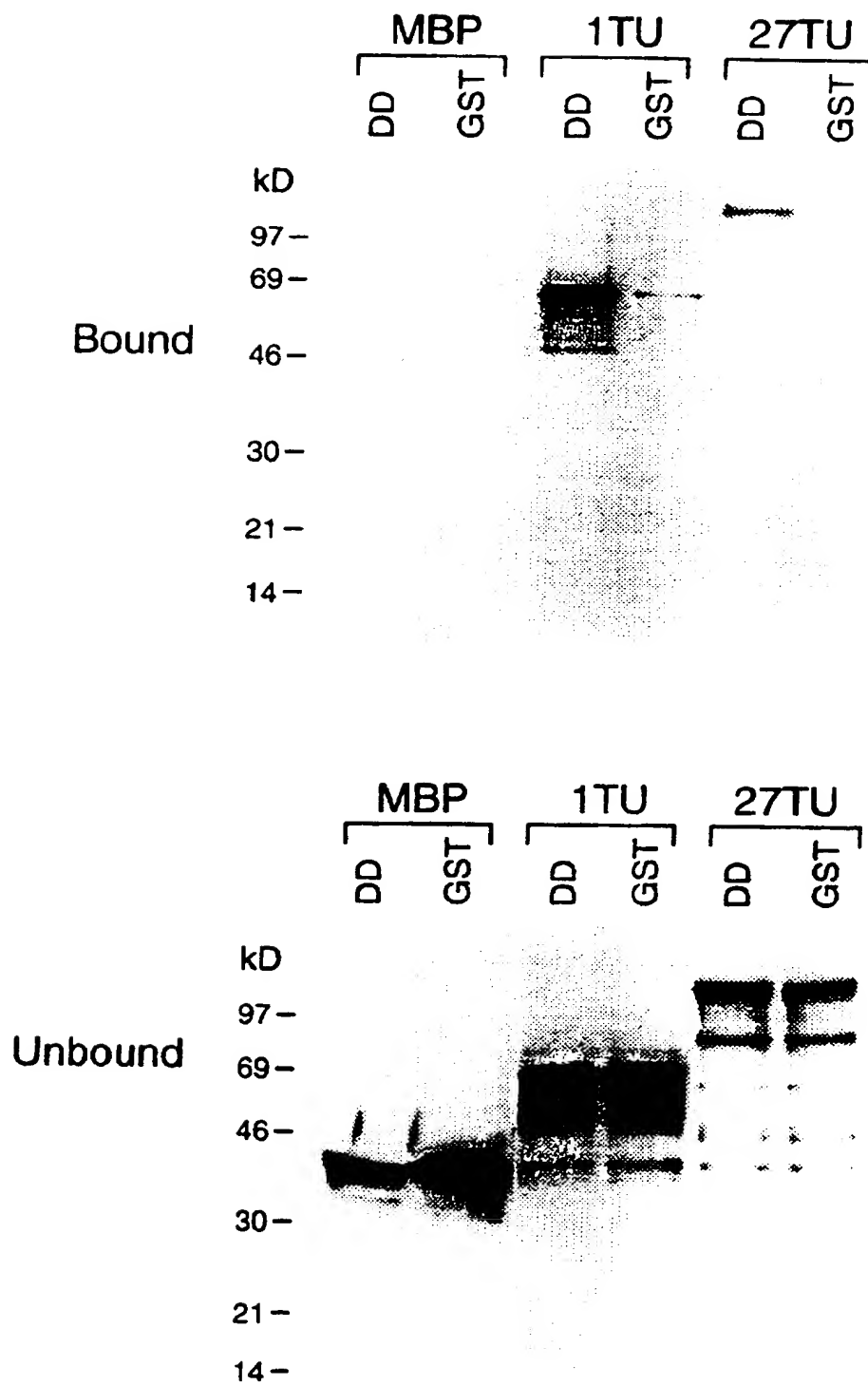




Fig. 5

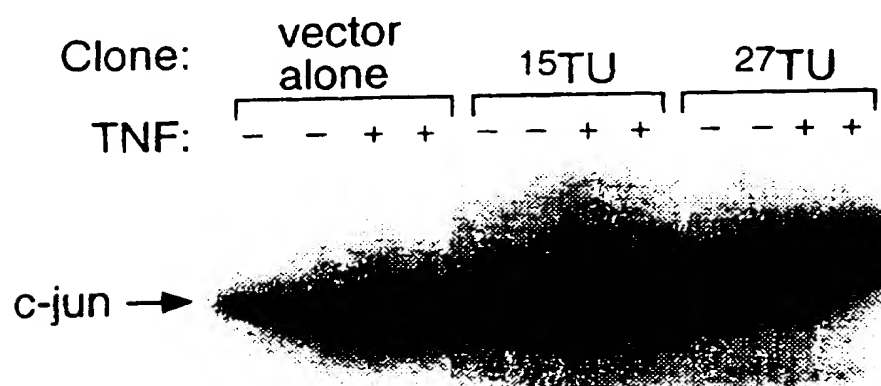
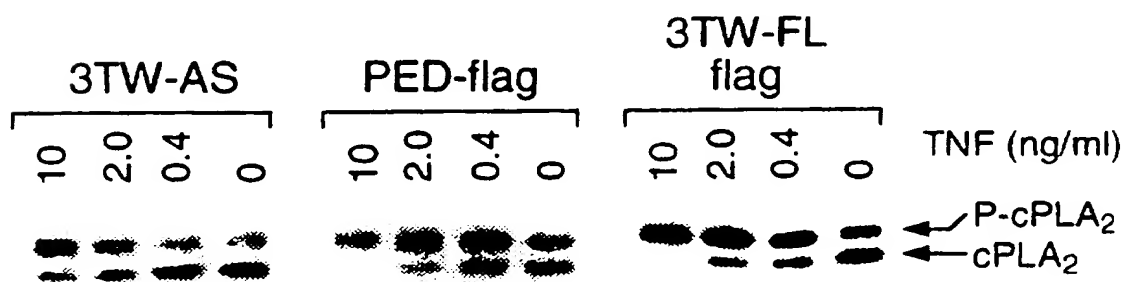


Fig. 6



Fig. 7



# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/02146

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K14/47 C07K14/715

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 95 31544 A (YEDA RESEARCH &amp; DEVELOPMENT CO. LTD) 23 November 1995</p> <p>see page 1, line 18-28</p> <p>see page 3, line 25 - page 4, line 13</p> <p>see page 5, line 3-29</p> <p>see page 9, line 3-20</p> <p>see page 11, line 1-7</p> <p>see page 11, line 27-34; examples 1-6</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1,4-8,</p> <p>12-14,26</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

6 June 1997

Date of mailing of the international search report

0 1. 07. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Mateo Rosell, A.M.

## INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/US 97/02146

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 16, 1991, MARYLAND, US, pages 10646-10653, XP000673586 S. SHIMASAKI ET AL.: "Identification of five different insulin-like growth factor binding proteins (IGFBPs) from adult rat serum and molecular cloning of a novel IGFBP-5 in rat and human" cited in the application see figure 4. see the whole document	25,26
P,X	--- WO 96 12735 A (GENETICS INSTITUTE INC.) 2 May 1996 cited in the application  see sequences 1-14, pages 33-57. See claims 1-35+ see the whole document	1-11,14, 15,17, 26,27, 29-38
P,X	--- WO 96 25941 A (YEDA RESEARCH & DEVELOPMENT CO. LTD.) 29 August 1996 see page 1, paragraph 1 see page 3, paragraph 2 see page 11, paragraph 3-4 - page 12, paragraph 1-5 see page 14 - page 15 see page 17 - page 18 see examples 3-6	1,8,13, 14,26
P,X	--- WO 97 03998 A (YEDA RESEARCH & DEVELOPMENT CO. LTD.) 6 February 1997 see pages 9-19 see abstract  -----	1,4-8, 13,14,26

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/02146

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16, 18-20, 23-24  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although these claims refer to a method of treatment of the human or animal body, the search was carried out and based on the alleged effects of the products.**
2. ☒ Claims Nos.: 1, 4-7  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**No other distinguishing feature has been provided for the problems of claim 1 than their ability to bind the death domain of the TNF-R1 receptor. For economical reasons, this makes a complete search impossible. The search was limited to real examples(seq.1-18) provided by the applicant**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 97/02146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9531544 A	23-11-95	AU 2546995 A	05-12-95
		CA 2189983 A	23-11-95
		EP 0759984 A	05-03-97
		FI 964509 A	09-01-97
		NO 964741 A	09-01-97
		ZA 9503842 A	17-01-96
WO 9612735 A	02-05-96	AU 3826195 A	15-05-96
WO 9625941 A	29-08-96	AU 5133296 A	11-09-96
WO 9703998 A	06-02-97	AU 4602296 A	03-07-96
		AU 6180596 A	18-02-97
		WO 9618641 A	20-06-96

